HUMAN PAPILLOMAVIRUS: TRENDS IN HUMAN PAPILLOMAVIRUS RATES, VACCINE UPTAKE, AND FACTORS DRIVING INTENTION TO VACCINATE

by

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted disease in the United States. It is also the primary cause of cervical cancer as well as other cancers. Fortunately, there are safe and effective vaccines to prevent HPV that are recommended for both men and women ages 9–26 years old. Unfortunately, vaccine uptake is considered low, leaving a need to increase HPV vaccine uptake across the U.S.

This study examines trends in high-risk HPV positivity rates over the past 10 years using large-scale laboratory test data, factors associated with vaccination in the published literature, and factors associated with intention to vaccinate in women age 18–26 years old in Utah.

Findings showed that HPV infection rates are likely falling, but at a rate that indicates less-than-optimal vaccination rates (consistent with CDC data). The trends in the published literature also indicate that intention to vaccinate is not increasing over time, and may actually be decreasing. Additionally, studies find physicians play a key role in influencing vaccination and are more likely to recommend to older woman. In Utah, physician's recommendation, age, religious practices, relationship status, and education level were associated with vaccine intention.

The results of this study can be used to inform future programs targeted at increasing HPV vaccination in Utah and perhaps in other low-vaccination states. For example, despite Advisory Committee on Immunization Practices (ACIP) recommendations for initiating HPV vaccination series in females aged 11 or 12 years,

and catch-up vaccination for females aged 13 through 26 years, we found that physicians are more likely to recommend vaccination at later ages. Additionally, our findings indicate that a strong physician recommendation significantly increases vaccination intention. These findings indicate the potential usefulness of a physician-focused intervention.

To Lindsay, Guy, and Cooper, for supporting me throughout this process.

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CHAPTER 1

INTRODUCTION

Human Papillomavirus (HPV) is the most common sexually transmitted infection in the United States, with peak prevalence among females 20–24 years of age (Dunne et al., 2007; Hariri et al., 2011; Satterwhite et al., 2013). It is now understood that infection with high-risk human papillomavirus strains is necessary for the development of cervical cancer and precancerous lesions (Bosch et al., 1995; Saslow et al., 2012). This implicates HPV in all cases of cervical cancer. Additionally, HPV plays a role in cancers of the head and neck (Fakhry & Gillison, 2006; Gillison & Lowy, 2004).

In 2006, the Food and Drug Administration (FDA) approved the first HPV vaccine. This was a quadrivalent vaccine (Gardasil®, Merck) offering protection against high-risk HPV (McLemore, 2006). Additionally, a second HPV vaccine, a bivalent vaccine (Cervarix®, GlaxoSmithKline) protecting against high-risk types 16 and 18, was approved in 2009 (Bouvard et al., 2009; Harper, 2009). Both vaccines have shown close to 100% efficacy and high observed effectiveness against HPV types 16 and 18, the cause of 70% of all cervical cancers (Centers for Disease Control and Prevention (CDC), 2012a; Markowitz et al., 2013). The Advisory Committee on Immunization Practices (ACIP) recommends vaccination for females 9 to 26 years old (Markowitz et al., 2007).

Since the time of initial vaccine approval, researchers have been modeling the potential impact the vaccine would have on the prevalence of covered HPV types

(Barnabas et al., 2006). However, HPV vaccination rates vary by state and are considered low in both adults and adolescents (CDC, 2013; Williams et al., 2014). These low vaccination rates would result in a more modest decline in HPV prevalence than would be seen with higher vaccination rates and would indicate a need for increased vaccination.

Surveillance

The first goal of this project is to design and evaluate a potential large-scale HPV surveillance system using national laboratory test data. Studies designed to monitor HPV infection, especially vaccine-preventable HPV types, and HPV-associated diseases can help determine the impact of HPV vaccines (CDC, 2012b). Comprehensive surveillance data are not readily available for genital HPV infection, as HPV infection is currently not nationally notifiable (CDC, 2012b; Weinstock, Berman, & Cates, 2004). Furthermore, HPV is considered *difficult* to estimate; that is, by criteria rating estimates of incidence and prevalence of STDs, rating of HPV is *III (poor)*. Inconsistent, nonrepresentative prevalence data and estimates are based on rough extrapolations (Weinstock et al., 2004). Data from this project may then be useful to observe trends that can help determine the impact of HPV vaccines (CDC, 2012b).

Meta-Analysis

The second goal of this study is to identify and amalgamate results of studies focusing on HPV vaccination, as many studies predicting HPV vaccination intention exist, but few studies exist to synthesize the many findings. While not the first meta-analysis regarding the HPV vaccine (Fisher, Trotter, Audrey, MacDonald-Wallis, & Hickman, 2013), the present meta-analysis adds to the literature by examining

physicians' intentions to prescribe the HPV vaccine. Additionally, the study examines individual and parental perceived safety and efficacy, physician recommendation, perceived severity, and/or perceived susceptibility to HPV, as predictors of intention to vaccinate young women. These synthesized findings will add to the current understanding of what drives HPV vaccination intention.

Utah Survey

The purpose of this third and final study is to assess the demographic and attitudinal factors that are associated with HPV initiation and completion among 18–26-year-old women in Utah. HPV vaccination rates vary widely by country and by state within the U.S. Vaccination rates are lower in Utah than the national average, with 24.7% of Utah adolescents completing the series (CDC, 2013). By contrast, more than 81% of eligible Utah children receive the tetanus, diphtheria, and acellular pertussis vaccine (Tdap) (Williams et al., 2014).

Our goal was to generate information that could be used to develop educational materials and intervention programs to increase HPV vaccination in women ages 18–26 specifically in Utah.

Study Setting, Data Sources, and Participants

Study One

The primary objective of study one is to estimate the positivity of high-risk HPV in the United States from 2004 to 2013 using retrospective data from HPV testing conducted at a National Reference Laboratory. These positivity rates and trends over time should reflect underlying prevalence rates in the population of women who undergo regular gynecological testing and should be useful in supplementing other nationwide

estimates of HPV vaccine impact.

Data from patient test results archived in an electronic data warehouse were extracted for HPV results from January 1, 2004 to June 1, 2013 to produce 757,761 female patient records with conclusive positive or negative results. Attached to each record were test results and demographic data, including age, sex, and client information. Using only the first observation for each patient per calendar year between 2004 and 2013, a longitudinal dataset was created, consisting of 735,437 total high-risk HPV results from 590,036 unique patients at 692 unique client sites in 48 U.S. states.

Study Two

Study two will consist of a meta-analysis and systematic review of the literature regarding 1) physician intention to recommend HPV vaccine, 2) individual or parental intention to receive HPV vaccine, 3) uptake of HPV vaccine, and 4) factors associated with individual and parental intention to vaccinate.

A systematic search of EMBASE, PsychInfo, Medline, PubMed, and Google Scholar identified 1,269 articles identified through database searches, of which 456 abstracts were reviewed and 306 were relevant for vaccine intention or uptake. Of these, 75 were included in the final analysis.

Study Three

This primary objective of study three is to study is to assess the demographic and attitudinal factors that are associated with HPV initiation and completion among 18–26-year-old women in Utah.

We recruited participants from the University of Utah Community Clinics through the University of Utah Primary Care Research Network. Participants were young women

aged 18–26 years who had a University of Utah Community Clinic visit in the previous 12 months. Potential participants were mailed a letter describing the project, a survey on attitudes toward the HPV vaccine, and a business reply envelope for easy return of the survey.

Specific Aims

Study One: Chapter 2

Primary Objective: To design and evaluate a potential surveillance system for human papilloma virus using reference laboratory data for the purpose of evaluating vaccine impact.

Study Two: Chapter 3

Primary Objective: To perform a systematic review, meta-analysis, and meta-regression of the existing literature on physician recommendation, intention, uptake, and factors driving intention to receive the HPV vaccine.

Study Three: Chapter 4

Primary Objective: To examine factors, as can be determined by a questionnaire, which are associated with stated vaccine uptake intentions to get vaccinated against HPV in women 18–26 years old in Utah.

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CHAPTER 2

SURVEILLANCE OF HUMAN PAPILLOMA VIRUS USING REFERENCE LABORATORY DATA FOR THE PURPOSE OF EVALUATING VACCINE IMPACT

Abstract

The purpose of this study is to present a method to estimate rate of change of high-risk HPV in the United States since 2004 in women using national reference laboratory data. Nationwide positivity rates of high-risk HPV for the United States before and since the introduction of an HPV vaccine in 2006 would provide insight into the uptake and impact of vaccination. These rate estimates would be representative of the sexually active population who undergo regular HPV screening – a target population for the HPV vaccine.

We extracted data for high-risk HPV testing results from January 1, 2004 to June 1, 2013 to produce 757,761 patient records of women between the ages of 14 and 59. Generalized linear models were created to assess differences in positivity between age categories and assess changes over time. Finite mixture models were used to investigate patterns within the distribution of time between sample collection and time of final result for all patients.

Positivity rates for the high-risk HPV group was 27.2% for all age groups combined. Highest rates occurred in individuals aged 14–19 and Hispanics. Data from 48

states and 692 sites were represented. While the positivity rates decreased for all age groups from 2004 to 2013, the 30 year and above age categories showed less of a downward trend following vaccine introduction, while the two age categories 20–24 and 25–29 showed a significantly different downward trend between pre- and postvaccine time periods (-0.1% per year to -1.5% per year, and 0.4 % per year to -1.5% per year, respectively). All other age groups had rates of change that became less negative, indicating a slower rate of decline.

Introduction

Numerous studies have demonstrated a clear causal relationship between human papillomavirus (HPV) and cervical cancer, with HPV considered necessary but not sufficient to cause cervical cancer (Bosch et al., 1995; Doorbar et al., 2012; Lowy & Schiller, 2006; McIntosh, Sturpe, & Khanna, 2008; Song, Pitot, & Lambert, 1999; Walboomers et al., 1999). HPV also plays a causative role in vaginal, anal, head, and neck cancers (Fakhry & Gillison, 2006; Gillison & Lowy, 2004, 2010; Zandberg, Bhargava, Badin, & Cullen, 2013). HPV includes over 100 subtypes and is divided into high- and low-risk groups according to oncogenic risk. In 2006, a quadrivalent vaccine (Gardasil®, Merck) offering protection against high-risk types 16 and 18 and low-risk types 6 and 11, was approved by the Food and Drug Administration (FDA). Additionally, a bivalent vaccine (Cervarix®, GlaxoSmithKline) protecting against high-risk types 16 and 18 was approved in 2009 (Bouvard et al., 2009). Both vaccines have shown close to 100% efficacy against HPV types 16 and 18, the cause of 70% of all cervical cancers (Centers for Disease Control and Prevention (CDC), 2012a). In June 2006, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination for females 9 to

26 years old (Markowitz et al., 2007). It is hypothesized that with good vaccination coverage, the prevalence of HPV and HPV-associated cancers will decline (Barnabas et al., 2006).

Although comprehensive surveillance for genital HPV positivity and prevalence data are considered difficult to estimate, several approximations exist (Satterwhite et al., 2013). A 2007 report showed that the overall prevalence in the U.S. of any HPV infection prior to vaccine introduction (2003–2004) was approximately 27% (Dunne et al., 2007). A follow-up study published in 2013 showed the overall rate from 2007–2010 was 40% (Markowitz et al., 2013). Both of these studies estimate national level prevalence, but were conducted on limited sample sizes (less than 5000 per time period), and had conflicting rates, with the 2013 study reporting a prevalence during the years 2003–2006 of 43% (Markowitz et al., 2013). Additional prevalence estimates exist, but these are often targeted at specific populations, lack sufficient sample size, are geographically isolated and often non-U.S. based (Banister et al., 2013; Dunne et al., 2013; Leinonen et al., 2013; Reiter et al., 2013; Škamperle, Kocjan, Maver, Seme, & Poljak, 2013; Walmer et al., 2013). Therefore, a need exists for surveillance with complete U.S. coverage to establish overall positivity and prevalence rates as well as trends in these rates (Centers for Disease Control and Prevention (CDC), 2012a; Wilson, Welch, & She, 2014).

The goal of this study is to estimate the positivity of high-risk HPV in the United States from 2004 to 2013 using retrospective data from HPV testing conducted at a national reference laboratory (ARUP Laboratories, Salt Lake City, UT). These positivity rates and trends over time should reflect underlying prevalence rates in the population of women who undergo regular gynecological testing and should be useful in supplementing

other nationwide estimates of HPV vaccine impact.

This study will illustrate that using such data can overcome the limitations of previous studies because the number of unique patients tested is large and account for a wide geographical spread. Additionally, since HPV testing is typically performed in conjunction with routine Papanicolaou (Pap) testing, and rates of routine testing are above 80% in U.S. women over 18 years of age, the data represent generalizable rates free from selection bias associated with testing typically performed to support clinical suspicion of disease (CDC, 2013).

Methods

Study Population and Analysis Datasets

This study was approved by the University of Utah Institutional Review Board. Samples are submitted to and tested by ARUP Laboratories for high-risk HPV (genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Data from patient test results archived in an electronic data warehouse were extracted for HPV results from January 1, 2004 to June 1, 2013 to produce 757,761 female patient records with conclusive positive or negative results. Attached to each record were test results and demographic data including age, sex, and client information. Using only the first observation for each patient per calendar year between 2004 and 2013, a longitudinal dataset was created, consisting of 735,437 total high-risk HPV results from 590,036 unique patients at 692 unique client sites in 48 U.S. states.

HPV Testing

Liquid-based endocervical samples were collected and submitted to ARUP Laboratories for HPV testing. Acceptable sample types include Digene® Cervical

Brushes (Qiagen, Hilden, Germany), ThinPrep® PreservCyt® media (Hologic, Inc., Marlborough, MA), and SurePath™ preservative (Becton-Dickinson, Franklin Lakes, NJ). Testing for HPV was performed according to manufacturer's instructions by the Digene® hc2 HPV DNA Test, which utilized Hybrid Capture 2 technology. ThinPrep® PreservCyt® samples were prepared using the Digene® HC2 Sample Conversion Kit.

Statistical Analysis

Positivity rates were analyzed by age category and year (both individual year and year categories: 2004–2007, 2007–2013) and compared. Frequency tables and exact binomial confidence intervals were constructed to present positivity rates (with 95% confidence intervals [CI]) by age category and year. Generalized linear models (GLM) were created to assess differences in positivity between age categories and assess changes over time (McCullagh & Nelder, 1989). Two- and three-way interaction models were used to assess both how rates have changed in the pre- and postvaccine eras and also how age category affects this pre- and postvaccine era effect on rate, respectively.

To account for potential bias associated with differences in ordering, several methods were employed. First, it was hypothesized that a positive bias might be associated with physicians who submit specimens for HPV testing based on abnormal cytology results (Shirts & Jackson, 2010). Therefore, finite mixture models were then used to investigate patterns within the distribution of time between sample collection and time of final result release for all patients (Figure 1) (Day, 1969; McLachlan & Peel, 2000). Positivity rates between these different testing patterns were compared. Additionally, sensitivity analyses were performed using GLM to assess the effects of time between visit, client size, and client consistency on positivity rates (McCullagh &

Nelder, 1989). Time between visits was calculated for patients with more than one visit as the average time between visits. Client size was calculated as number of tests ordered overall and for each year. Client consistency was an indicator variable representing whether or not a client had ordered tests both at the beginning and end of the study period (tests ordered in 2004 and 2013). These derived variables were compared for both their main effect on positivity rate and interaction effects with time on positivity rates.

All calculations were performed using SAS software (v9.3, SAS Institute Inc., Cary, NC, USA). Results were considered statistically significant if $p<0.05$.

Results

Raw Positivity Rates: High-Risk HPV

Positivity rates for high-risk HPV were separated and compared across time and by age groups (Table 1). Overall the positivity rate in women aged 14 to 59 years from 2004 to 2013 (n=735,437) was 27.2% (95% confidence interval [CI], 27.1 to 27.3). When separated by time period, the positivity rates decreased over time, with the prevaccine introduction period (2004 to 2006) having an overall positivity rate of 35.3% (95% CI, 35.1 to 35.5) and the final time period (2011 to 2013) having an overall positivity rate of 19.7% (95% CI, 19.5 to 19.9).

When separated by age group, each showed a significant decline in overall positivity over time. The largest absolute decrease was in the 30 to 39 year old age group, with a decrease from 27.2% (95% CI, 26.7 to 27.6), in the years 2004 to 2006, to 16.3% (95% CI, 16.1 to 16.6), in the years 2011 to 2013. The smallest absolute decrease was in the 25 to 29 year old age group, with a decrease from 44.0% (95% CI, 43.4 to 44.6), in the years 2004 to 2006, to 42.7% (95% CI, 41.9 to 43.4), in the years 2011 to 2013 (Table

1). Overall, current rates were highest in both the 14 to 19 year old and 20 to 24 year old age categories, with the positivity rate being 54.5% (95% CI, 52.9 to 56.2), and 54.7% (95% CI, 54.0 to 55.5), respectively in the years 2011 to 2013.

Factors and Significance of Bias

To establish if physician ordering practices influenced positivity, it needed to be determined if an indication for ordering HPV testing was present prior to sample submission. This was accomplished by analysis of the difference in collection time (reported by the client) and the result time (time at which results are reported from ARUP Laboratories). Finite mixture models were used and established two distinct populations of patient samples submitted; a population with a peak resulting time minus collection time at 3 days, and another at 8 days (Figure 1). A nadir (antimode) in the mixture model was observed at 5 days, which was then used as the cutoff between pattern 1 datasets (<5 days) and pattern 2 datasets (>5 days). This is consistent with previous studies conducted at ARUP Laboratories and matches data that the majority of cytological results on Pap specimens are completed within 5 days (Clary et al., 2013; Shirts & Jackson, 2010). We also examined the subset of cases with both HPV test and Pap smear results to validate our assumption that HPV testing delayed beyond 5 days was likely the result of abnormal cytology results. This subset (n = 9,347) showed a bimodal peak, with normal cytology results associated with HPV test results on average 6 days later, whereas abnormal cytology results had HPV results reported on average 8 days later. Therefore, it is hypothesized that samples in the pattern 2 dataset were submitted with suspicion of HPV as a result of abnormal cytological findings and should be excluded from our estimates of HPV prevalence. Positivity rates support this, as they are significantly higher in pattern 2

compared to pattern 1 in all age groups across all years (Tables 1, 2). Additionally, sensitivity analyses performed using general linear models showed no statistically significant effect of time between visit, client size, and client ordering consistency on positivity rates.

Trends: High-Risk HPV

Following investigation of potential influences on the positivity rate and determining if they had significance or not, it was estimated that the positivity rates in pattern 1 should provide a useful indicator of underlying population prevalence of sexually active women getting regular gynecological screening. Overall positivity in this pattern 1 group of high-risk HPV for women aged 14 to 59 years from 2004 to 2013 was 19.4% (95% CI, 19.3 to 19.6). Over time, the positivity rates decreased from 31.6% (95% CI, 31.2 to 32.0) during the years 2004 to 2006, to 13.2% (95% CI, 13.0 to 13.4) during the years 2011 to 2013.

Women aged 14 to 19 years showed the largest absolute decrease in the pattern 1 group in positivity from 55.5% (95% CI, 54.0 to 56.9) during the years 2004 to 2006, to 43.0% (95% CI, 40.0 to 45.9) during the years 2011 to 2013. Women aged 50 to 59 showed the largest percent decrease, dropping 49.7% in prevalence from 12.4% (95% CI, 11.6 to 13.2) during the years 2004 to 2006, to 6.2% (95% CI, 5.9 to 6.6) during the years 2011 to 2013. The smallest percent decrease was seen in women aged 20 to 24, with only an 18.0% reduction in positivity from 54.1% (95% CI, 53.1 to 55.1) during the years 2004 to 2006, to 44.4% (95% CI, 43.0 to 45.8) during the years 2011 to 2013.

Rates of change in high-risk HPV positivity per year were calculated and compared between the prevaccination (2004–2006) and postvaccination periods (2007–

2013) in all age groups. Generalized linear models showed that age category had a significant effect on rates when these time periods were compared. In the pattern 1 group, all age categories showed positivity decreases in the postvaccine period; however, only women aged 20 to 24 and 25 to 29 showed negative differences (-1.4% per year and -1.9% per year, respectively) when pre- and postvaccine period rates of change were compared. All other age categories had rates of change that were less negative, and closer to zero (Figure 2, Table 2).

Discussion

The goal of this study was to estimate the current positivity of and trends in high-risk HPV in women in the United States from 2004 to 2013; specifically, in women who undergo regular gynecological screenings. These data indicate that the overall positivity of HPV is declining, especially in young women; however, the rate at which positivity is declining is slower than other studies indicate in certain age categories (Markowitz et al., 2013). This may be a combination of insufficient vaccination coverage as well as these data being a mixture of vaccine-preventable and other high-risk types collectively. Mathematical models have predicted that the introduction of the vaccine should have a strong impact on HPV positivity rates in the types covered by the vaccine (Barnabas et al., 2006). While this data could not be separated entirely by type, a reduction of 18 to 25% in positivity in all high-risk HPV was seen in women aged 14 to 29 when comparing rates prior to the vaccine introduction (2004 to 2006) to current rates (2011 to 2013).

While most studies performed to determine HPV positivity or prevalence rely on survey-based methods, this study has several strengths that allow for the generalizability of the results to women who undergo regular gynecological screening in the US. First, the

data were retrospective data from a large national reference laboratory, which created a large dataset of more than 700,000 high-risk HPV results that accurately reflected at-risk and vaccine-targeted population. Second, the data were filtered in several ways: only the first visit per calendar year of each patient was used to reduce redundancy that may occur as a result of repeat confirmatory testing, and potential ordering bias was reduced by separating results from patient samples believed to be submitted because of abnormal cytology results. To account for ordering bias, finite mixture modeling was used to determine where, if any, a separation may exist between the time the samples were collected and the time that results were entered (Day, 1969). The separation observed is likely the result of samples being immediately sent for HPV testing versus samples that had been screened for abnormal cytology before being sent for HPV testing (Shirts & Jackson, 2010). The cutoff between pattern 1 and 2 of 5 days can be further supported by a 2013 survey by the College of American Pathologists (CAP) that showed that 83.9% of Papanicolaou testing took less than 5 days to completion, with the majority taking 3 to 4 days (Clary et al., 2013). Additionally, the positivity rates in testing pattern 2 were significantly higher than in testing pattern 1, suggesting physicians had an indication for ordering HPV testing, such as abnormal Pap smear results. Lastly, sensitivity analyses were performed to determine if differences in clients might influence the positivity rates. Since these data included many individual client sites, it was theorized that differences in client size might account for a bias in positivity: clients with fewer sample submissions may be targeting at-risk individuals with a higher likelihood of disease. Using generalized linear models, it was shown that there were no differences in positivity rates when adjusting for client size, location, or ordering trends, further supporting that the

positivity rates truly are indicative of overall prevalence.

Based on retrospective data from a national reference lab from 2004 to 2013, the overall positivity of high-risk HPV in all age groups was 27.2%. Looking at only pattern 1, which was established as an estimate of unbiased prevalence, the rate drops to 19.4%. Our estimate of prevaccine high-risk HPV positivity in women 14 to 59 years old was 31.6%, compared to the rates reported from other studies of 15 – 29% (Dunne et al., 2007; Markowitz et al., 2013). For the current time period (2010–2013), the positivity rate decreases to 13.2% for all women aged 14 to 59. By age group, our positivity estimates are also higher, particularly in the 14-19 year old group (55–57%) when compared to CDC data (15–20%). This could be due to the fact that HPV testing is generally only performed for sexually active women; so positivity estimates in this study likely reflect the positivity rates in the sexually active population, which has been shown to be close to 50% in young adult females, similar to the present study (Dunne et al., 2007; Markowitz et al., 2013). Furthermore, the method of specimen collection differed from other studies in that provider-collected cervical swabs were used as opposed to self-collected cervicovaginal swabs. Provider collection could not feasibly be standardized in this study, but overall performance of HPV testing has been shown to be similar for both collection methods (Snijders et al., 2013).

It is important to note that despite a decline in high-risk HPV positivity in all age categories, the rate of positivity change per year is not consistent. HPV vaccination is only recommended in women up to the age of 26; therefore, this group would likely have a faster decrease in positivity. It could further be postulated that, since the vaccinated population is increasing in age, an inverse relationship between age and change in

prevalence per year would exist. This was observed, with the postvaccine introduction period rates of positivity change per year being consistent in the vaccine target group (age groups 14 to 19, 20 to 24, and 25 to 29) at a -1.5% and decreasing with each increase in age category to a low of -0.3% in the 50 to 59 year old group. The decreasing rates that were seen in the prevaccine introduction period are likely due to inconsistent testing practices among physicians and an increasingly heterogeneous population being screened; however, these rates still provide a baseline to compare postvaccine period rates. Crucially, the difference in the pre- and postvaccine era rates of positivity change were only more negative in the age groups that had overlap in vaccine and screening guidelines (20 to 24 and 25 to 29-year-old women). This suggests that the decreases in the rates of prevalence change per year seen in the younger population age categories could be due to increasing vaccination rates.

For comparison, 618,261 Chlamydia tests were analyzed for females stratified by the same age categories as for HPV and covering years 2004–2013 (Figure 3). Across all age categories, there is no significant downward trend in positivity rates and, in fact, most age categories show an upward trend (especially since 2008). These results further support the hypothesis that downward trends observed in HPV are likely attributable to vaccine uptake.

Several limitations to this study exist. Current guidelines recommend screening every 3 years in all sexually active women over 21 years of age; therefore, and as a result of the data being collected at a national reference lab, the population represented is likely a sexually active population with access to healthcare. Furthermore, cervical cancer screening guidelines have changed over the duration of data collection, with the

introduction of co-testing HPV and Pap screening in women older than 30 years and recommendation against screening in women less than 21 years regardless of first sexual contact (Committee on Practice Bulletins—Gynecology, 2012; Saslow et al., 2012). Despite these changes, these data and several studies indicate that the guidelines are not being followed as testing is still frequently performed on an annual basis, in women under 21 years of age, and in women following hysterectomy (Kepka, Breen, King, Benard, & Saraiya, 2014; Roland et al., 2013; Shirts & Jackson, 2010). Another final limitation is that the Hybrid Capture 2 method does not differentiate genotypes and differentiation of specific high-risk vaccine preventable HPV strain was not possible (Castle et al., 2008; Sargent et al., 2010).

We attempted to mitigate some of the potential biases by focusing on collection pattern 1 (results within 5 days of collection) and only including one visit within the calendar year, but future studies of this kind will certainly be needed to both validate and improve upon methodology. Additional studies that have access to multiple testing sites may be able to refine analyses by using characteristics of the different client sites: for example, differences in ordering volumes, within-center positivity rates, or information collected outside of the analytic framework, such as clinical indications for testing in their population. Our study demonstrates the potential for using HPV test data from large national reference laboratories to supplement the ongoing and planned efforts to monitor HPV vaccine impact in the US (Markowitz et al., 2010).

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Table 1. Positivity of High-Risk HPV According to Age and Year Group in Pattern 1 Individuals from a National Reference Laboratory

Age (years)	2004–2013		2004–2006		2007–2010		2011–2013	
	No.	Positivity (%)	No.	Positivity (%)	No.	Positivity (%)	No.	Positivity (%)
Overall	256,683	19.4	51,080	31.6	119,896	18.6	85,707	13.2
14–19	10,979	50.6	4,692	55.5	5,224	47.8	1,063	43.0
20–24	25,725	50.2	9,276	54.1	11,525	49.5	4,924	44.4
25–29	24,363	36.8	7,545	41.2	11,219	36.8	5,599	30.8
30–39	77,928	15.7	12,439	24.4	36,104	15.1	29,385	12.7
40–49	67,841	9.5	10,824	14.7	31,955	9.0	25,062	8.0
50–59	49,847	7.4	6,304	12.4	23,869	7.1	19,674	6.2

Table 2. Average Rate of Change Is Positivity per Year Comparing Pre- and Postvaccine Periods

Age, years	2004–2006	2007–2013	Difference
14–19	-2.2	-1.5	0.7
20–24	-0.1	-1.5	-1.4*
25–29	0.4	-1.5	-1.9*
30–39	-3.0	-0.8	2.2*
40–49	-1.7	-0.4	1.3*
50–59	-1.4	-0.3	1.1*

* $p < .05$.

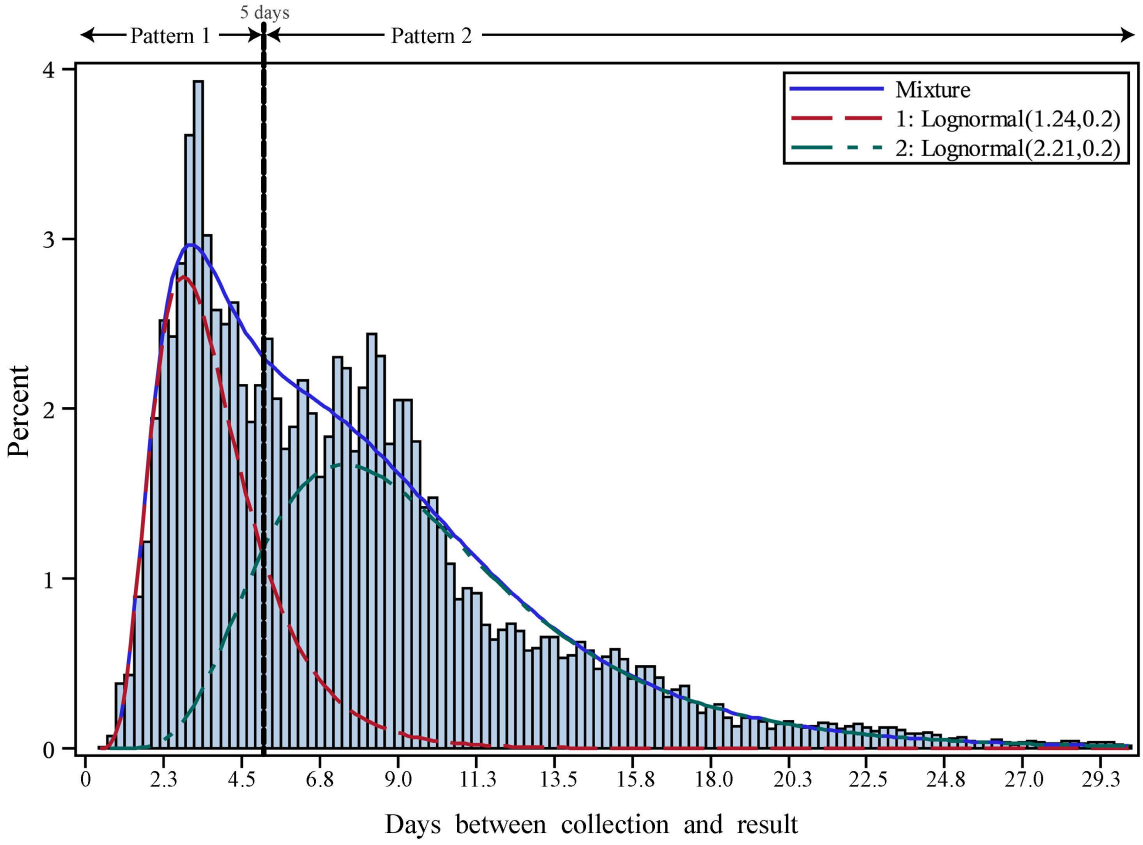

Figure 1. Finite Mixture Modeling (FMM) of Time between Collection and Final Result Indicating Distinct Distributions

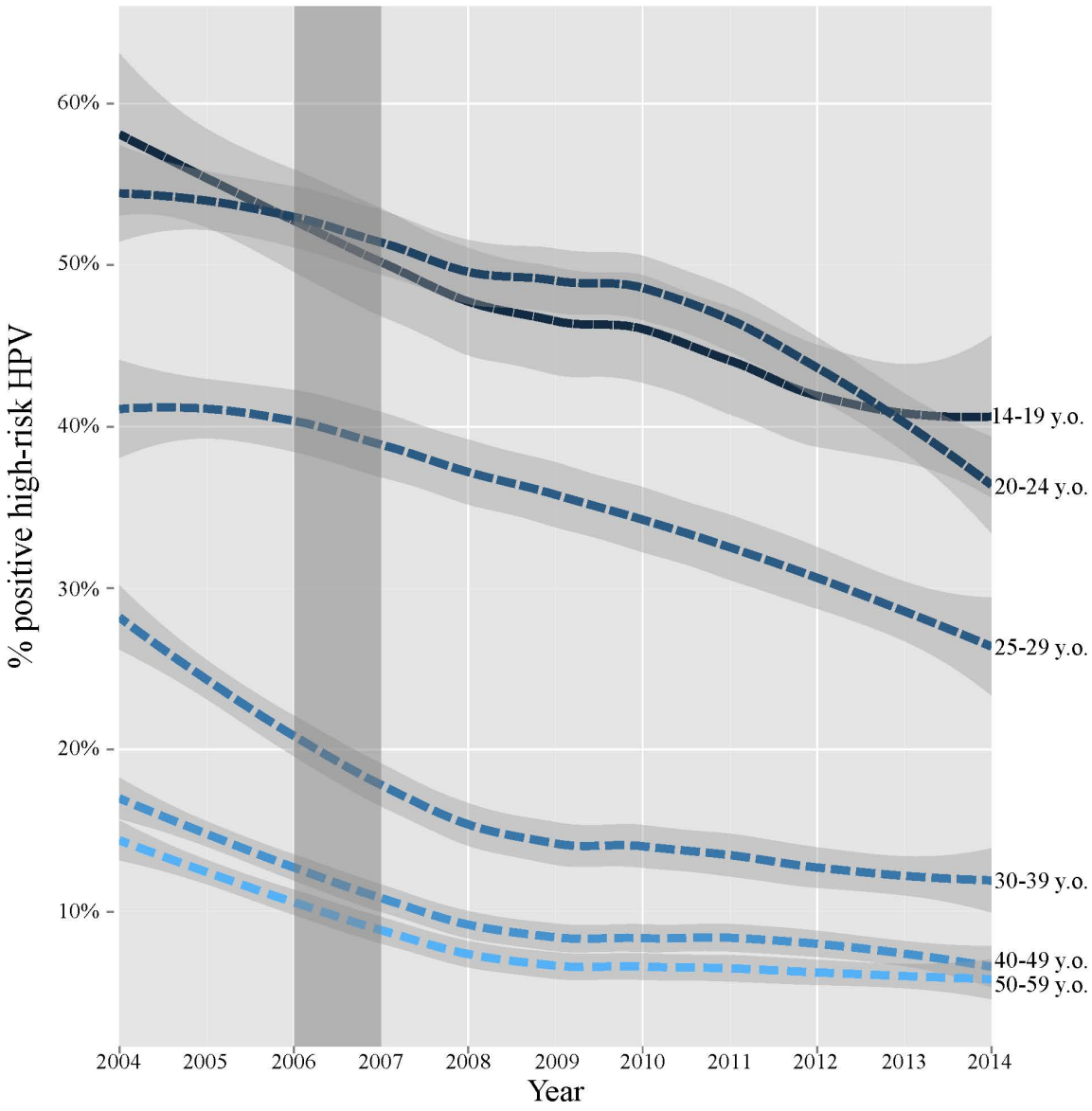

Figure 2. High-Risk HPV Positivity in Pattern 1 Individuals by Year and Age Category from a National Reference Laboratory

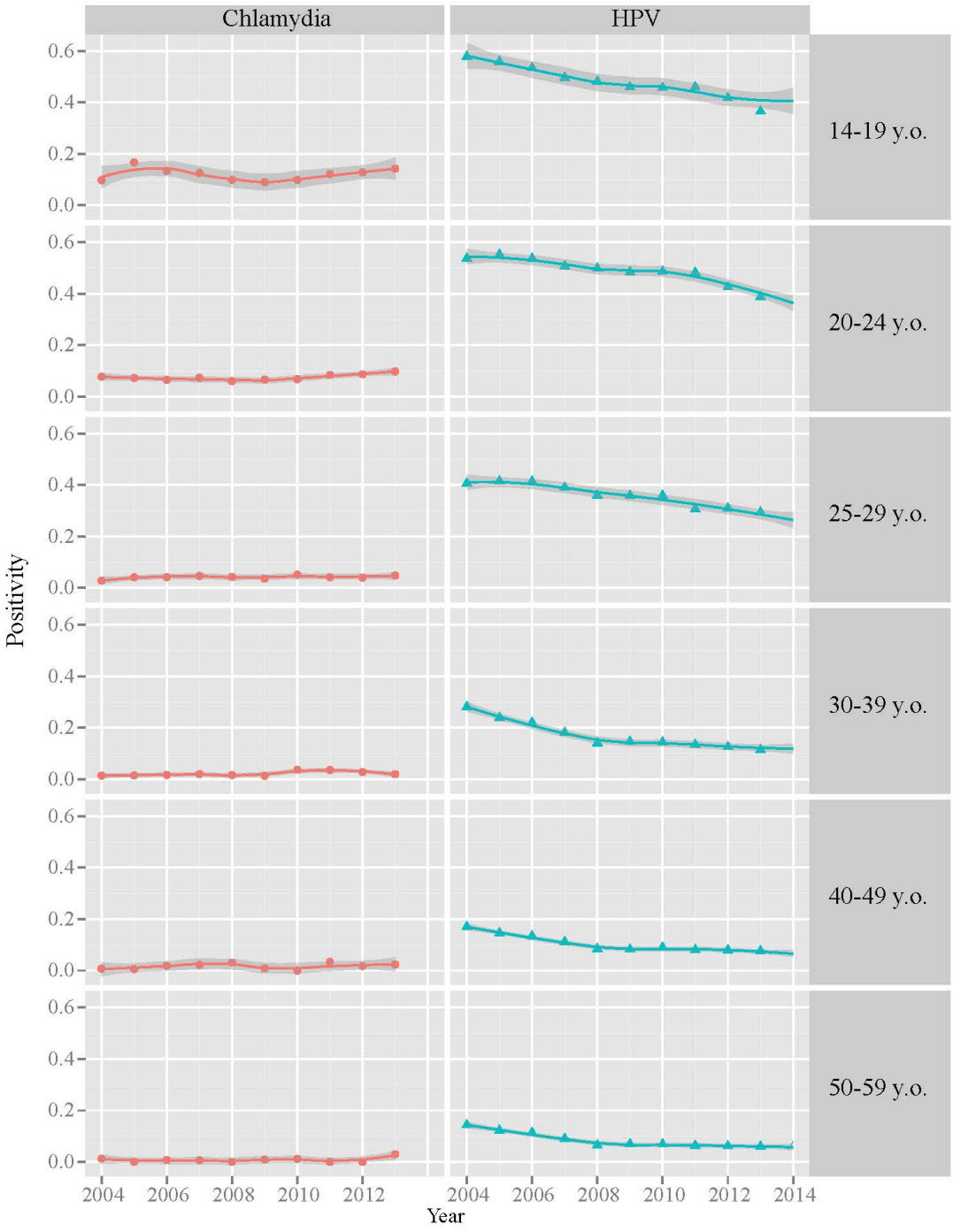

Figure 3. Comparison of Positivity Rates between High-Risk HPV (Pattern 1 Individuals) and Chlamydia by Year and Age Category from a National Reference Laboratory

CHAPTER 3

FACTORS PREDICTING HUMAN PAPILLOMAVIRUS VACCINATION INTENTION AND UPTAKE: A META-ANALYSIS AND SYSTEMATIC REVIEW

Abstract

Background

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. It is the primary cause of cervical cancer and is associated with cancers of the vulva, vagina, penis, and anus; additionally, HPV can cause oropharyngeal cancer. Despite the availability of effective vaccines, vaccination rates remain low. Many studies predicting vaccination intention exist, but few studies exist to synthesize the many findings.

Methods

Our database search strategy identified 1269 studies relating to physician recommendation, parental and individual intention, uptake, and factors relating to individual intention to receive the HPV vaccine. Three reviewers independently abstracted data and discrepancies were resolved by consensus between abstractors. All meta-analyses used random effects models with restricted maximum-likelihood (REML) to estimate between study variance. Subgroup analysis and meta-regression analysis were performed to investigate and reduce heterogeneity where heterogeneity was high.

Results

Of the 1,269 articles identified through database searches, 456 abstracts were reviewed and 306 were relevant for vaccine intention or uptake. Of these, 74 were included in the final analysis.

For studies that considered physician recommendation, physicians were very likely to recommend or prescribe the HPV vaccine. However, this proportion varied significantly by the age category of the intended recipient, with physicians more likely to recommend or prescribe to older children and more likely still to recommend or prescribe for adults.

We also summarized studies involving overall parental intention to vaccinate children, individual's intention to vaccinate themselves, vaccine uptake, and odds ratios of factors predicting parental and individual intention to vaccinate and vaccine uptake.

Conclusions

Despite Advisory Committee on Immunization Practices (ACIP) recommendations for routine HPV vaccination of females aged 11 or 12 years, and catch-up vaccination for females aged 13 through 26 years, we found that physicians are more likely to recommend vaccination at later ages.

Additionally, findings on parental and individual intent and uptake and factors that drive them might better inform future interventions aimed at increasing HPV vaccination rates.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and worldwide (Hariri et al., 2011; Lynde, Vender, & Bourcier). It is

currently considered the primary cause of cervical cancer (Bosch et al., 1995; Walboomers et al., 1999). Recognition of the link between HPV and cervical cancer led to the development of vaccines designed to prevent infection with certain high-risk types of HPV (Harper, 2009; Lowy, & Schiller, 2006; McLemore, 2006). The most prevalent HPV types (6, 11, 16, and 18) cause up to 70% of all cervical cancers (HPV16 and 18) and about 90% of genital warts (HPV6 and11) in young women ages 9–26 years (Dunne et al., 2013; Škamperle, Kocjan, Maver, Seme, & Poljak, 2013). In 2006, the Food and Drug Administration (FDA) approved Merck's Gardasil® vaccine in girls and women ages 9–26 years (McLemore, 2006). This vaccine proved highly effective in preventing these four types of HPV. A second HPV vaccine, Cervarix®, developed by GlaxoSmithKline, targets the two most common HPV types associated with cervical cancer (HPV16 and 18; Harper, 2009).

HPV vaccination rates vary by country and also by state within the U.S. Rates are considered low with only 34.8% of adolescent females in the U.S. having completed the vaccine series (3 doses) in 2011 (Centers for Disease Control and Prevention [CDC], 2013; Williams et al., 2014). By contrast, more than 85–90% of eligible children in the U.S. are compliant with the Measles-Mumps-Rubella (MMR) series (Williams et al., 2014). The CDC has named increasing HPV vaccination rates one of its top five priorities in 2014 (Greenberg, 2014).

Hundreds of studies have been performed to investigate predictors of HPV vaccine intention and uptake in hopes of improving vaccination rates. However, as the number of studies increases, the need to organize and synthesize findings increases as well. To amalgamate results from the literature, we conducted a meta-analysis and systematic review of the current literature on HPV vaccination intention/uptake. While

not the first meta-analysis regarding the HPV vaccine (Fisher et al., 2013), the present meta-analysis adds to the literature by examining physicians' intentions to prescribe the HPV vaccine. Additionally, the study examines individual and parental perceived safety and efficacy, physician recommendation, perceived severity, and/or perceived susceptibility to HPV, as predictors of intention to vaccinate young women. These synthesized findings will add to the current understanding of what drives HPV vaccination intention.

Methods

Data Collection

We followed the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines throughout the design, execution, and reporting of this study (Stroup et al., 2000). The key outcomes for this study were: a) reported proportion of physicians who intend to prescribe HPV vaccine, b) reported proportion of parents who intend to have their child receive the vaccine, c) reported proportion of individual women who intend to receive the vaccine themselves, and d) factors that predict intention to receive the HPV vaccination. Studies were included in the final analysis if they either included a reported count or proportion of physicians who intend to recommend the HPV vaccine, of parents who intend to get the HPV vaccine for their children, of individuals who either intend to receive the vaccine in the future or who have received the vaccine, or a reported odds ratio with 95% confidence interval for one or more of the key factors involved with intention to vaccinate, e.g., the increased odds of intention to vaccinate given a physician's recommendation.

A systematic search of EMBASE, PsychInfo, Medline, PubMed, and Google Scholar was performed using relevant medical subject heading (MeSH) terms related to:

- Papillomavirus
- HPV vaccine
- Vaccination
- Immunization
- Intention
- Uptake

Data Abstraction

Proportions and odds ratios were abstracted by five reviewers (AW, AG, CCC, MJE, and AJ) and then double-checked independently by three reviewers (ARW, ATG, and CCC), with disagreements in abstracted values settled by consensus. For odds ratios, adjusted ORs were recorded when available; otherwise, crude ORs were recorded. Each paper was assigned a subjective quality score, ranging from 1–5, based on average of three reviewers' scores (AW, AG, MJE). These scores were then converted to "high," "moderate," and "low" potential for bias from the average of the three reviewers. Agreement in quality assignment was greater than 80%. However, these scores were not used to exclude studies or used in analysis, as it has been proposed such use can actually introduce a source of bias (Greenland & O'Rourke, 2001).

Assessing Heterogeneity

Heterogeneity between studies was tested using Cochran's Q statistic and the proportion of heterogeneity due to variation between studies was quantified using the I^2 statistic (Higgins & Thompson, 2002; Schulze, Holling, & Böhning, 2003). The value of I^2 describes the percentage of variability in point estimates that is due to heterogeneity rather than sampling error (Higgins & Thompson, 2002). Negative values of I^2 were set

equal to zero, so that I^2 lay between 0% and 100%, where a value of 0% indicated little or no observed heterogeneity, and larger values showed increasing heterogeneity (Higgins & Thompson, 2003). Besides quantifying the amount of heterogeneity present, we tried to explore the potential causes of the heterogeneity. We did this visually by using forest plots, and analytically using subset analysis and meta-regression to investigate whether particular covariates explained a substantial proportion of the heterogeneity of effects between studies (Thompson & Higgins, 2002). For proportions and odds ratios, we considered the following as possible covariates: year study data were collected, age of potential vaccine recipient, and country or continent of study origin. Covariates were considered both in terms of statistical significance and reduction in heterogeneity, i.e., reduction in I^2 value.

Statistical Amalgamation

Binary estimates for proportion intending to vaccinate were calculated by taking the exact binomial proportion and standard error of the number of those declaring intention or uptake over total number of participants within the study. Calculation of an overall proportion of physicians intending to recommend HPV vaccine was performed using random effects meta-analysis of single proportions using logit transformation (Viechtbauer, 2010). Calculation of overall odds ratios for individual predictors was performed using meta-analysis, applying generalized linear (mixed-effects) models (Van Houwelingen, Zwinderman, & Stijnen, 1993; Viechtbauer, 2010). For both proportions and odds ratios, restricted maximum-likelihood estimators were used to estimate the between-study variance τ (Hariri et al., 2011; Viechtbauer, 2010).

Amalgamation of main effects, tests of study heterogeneity, and subgroup analysis where performed using the metaphor package for R (version 3.0.2; R Core Team

(2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/ (Viechtbauer, 2010).

Results

Of the 1,269 articles identified through database searches, 456 abstracts were reviewed and 306 were relevant for vaccine intention or uptake. Of these, 74 studies met all inclusion criteria for our analysis. A flow chart for this selection schema is presented in Figure 4 and descriptions of included studies are given in Table 3.

Physician's Intention to Prescribe HPV Vaccine

There were six studies on physician endorsement or recommendation of the HPV vaccine (Barnack, Reddy, & Swain, 2010; Duval et al., 2007; Feemster, Winters, Fiks, Kinsman, & Kahn, 2008; Henninger, 2009; Kahn et al., 2005; Kahn et al., 2008). The proportion of physicians who intended to prescribe the HPV vaccination ranged from 66% to 97%. However, there was a high degree of heterogeneity (overall $I^2 = 96.4\%$) between studies (Figure 5). A significant amount of heterogeneity could be attributed to the age of intended recipient, with physicians more likely to recommend vaccination to older girls. The proportion of physicians likely to vaccinate were 73% (95% CI: 68%-78%), 89% (95% CI: 76%–95%), and 95% (95% CI: 84%–98%) for recipients aged less than 14 years, 14–17 years, and greater than 17 years, respectively (p=0.0014). Still, heterogeneity was high within these age categories and specific estimates of pooled effects should be used with care.

Parents' Intention to Have Daughters Vaccinated

Overall, 26 studies reported parents' intention to vaccinate their daughters: 15 studies conducted in the U.S. (Allen et al, 2010; Askelson et al., 2010; Barnack et al, 2010; Bernat, Harpin, Eisenberg, Bearinger, & Resnick, 2009; Constantine & Jerman, 2007; Dempsey, 2009; Fazekas, Brewer, & Smith, 2008; Gerend, Weibley, & Bland, 2009; Gottlieb et al., 2009; Guerry et al., 2011; Litton, Desmond, Gilliland, Huh, & Franklin, 2011; Perkins, Pierre-Joseph, Marquez, Iloka, & Clark, 2010; Podolsky, Cremer, Atrio, Hochman, & Arslan, 2009; Rahman, Elam, Balat, & Berenson, 2013; Rosenthal et al, 2008) and 11 studies conducted outside the U.S. (Brabin, Roberts, Farzaneh, & Kitchener, 2006; Dinh et al., 2007; Hofman et al., 2014; Korfage, Essink-Bot, Daamen, Mols, & van Ballegooijen, 2008; Lenselink et al., 2008; Marlow, Waller, & Wardle, 2007; Ogilvie et al., 2007; Sam et al., 2009; Tozzi et al., 2009; Woodhall et al., 2007). Of the 26 studies reporting parental intention to vaccinate, 9,973 out of 13,831 parents (72.1%) reported intention to vaccinate their daughter against HPV. This proportion was higher in studies outside the U.S. (84%) compared to studies conducted inside the U.S. (61%) (Figure 6). Of the 21 studies reporting vaccine uptake in women, 256,246 out of 498,266 (51.4%) had received (adult women) or reported that their daughter had received (young women) one or more HPV shot. There was high heterogeneity between studies (I^2=98.4%) (Figure 6). There were significant differences between intention proportions from studies conducted within the U.S. versus studies conducted outside the U.S. (p=0.0165), with studies in the U.S. reporting lower intentions (Table 4). There was also a downward trend in parental intention by study year; however, trend rates, adjusted for age of intended recipient and whether or not study was conducted in U.S., were not statistically significant (Figure 7, Table 4). After adjusting for age of

intended recipient and whether study was conducted within or outside the U.S., heterogeneity was substantially reduced from 98.4% to 16.3%.

Individual Women's Intention to Receive Vaccine for Themselves

There were 25 studies that focused on individuals' intention to receive the HPV vaccine for themselves (Allen et al., 2009; Blumenthal et al., 2009; Casey, Crosby, Vanderpool, Dignan, & Bates, 2013; Chan, Yan, Lo, Cheung, & Hung Chung, 2009; Christian, Christian, & Hopenhayn, 2009; Cui, Baldwin, Wiley, & Fielding, 2010; Di Giuseppe, Abbate, Liguori, Albano, & Angelillo, 2008; Forster, Marlow, Wardle, Stephenson, & Waller, 2010; Gerend, Lee, & Shepherd, 2007; Gerend & Magloire, 2008; Hsu et al., 2009; Jones & Cook, 2008; Juraskova, Bari, O'Brien, & mcCaffery, 2011; Kahn, Rosenthal, Hamann, & Bernstein, 2003; Katz et al., 2009; Kwan et al., 2009; Kwan, Tam, Lee, Chan, & Ngan, 2011; Li et al., 2009; Moreira et al., 2006; Mortensen, 2010; Watts et al., 2009; Wong, 2008; Wong & Sam, 2010; Woodhall et al., 2007; Young et al., 2010). Although overall intention appears high, there was a high degree of heterogeneity between studies (I^2 = 98.8%) and intention estimates ranged broadly from 26% to 89%, depending on the study (Figure 8). However, much of the heterogeneity could be attributed to country of study and year data were collected. After adjusting for age of intended recipient and whether study was conducted within or outside the U.S., heterogeneity was substantially reduced from 98.8% to 14.3% (Table 5). Additionally, there was a significant downward trend in individual intention to vaccinate by study year (-4%/year; p-value = 0.0112) after adjusting for age of intended recipient and whether or not study was conducted in U.S. (Table 5, Figure 9).

Uptake

Overall, 21 studies reported HPV vaccine uptake (1+ doses) (Brewer et al., 2011; Caskey, Lindau, & Alexander, 2009; Fisher et al., 2013; Gottlieb et al., 2009; Guerry et al., 2011; Jain et al., 2009; Kahn et al., 2008; Kang & Moneyham, 2010; Laz, Rahman, & Berenson, 2013; Li et al., 2013; Mathur, Mathur, & Reichling, 2010; Mortensen, 2010; Perkins et al., 2010; Rahman et al., 2013; Reiter, Brewer, Gottlieb, McRee, & Smith, 2009; Spencer Nee Pilkington, Brabin, Verma, & Roberts, 2013; Steens et al., 2013; Stöcker, Dehnert, Schuster, Wichmann, & Deleré, 2013; Taylor et al., 2014; Tsui et al., 2013). Heterogeneity was extremely high between studies (I^2 = 99.8%). Meta-regression indicates a significant association between age (in years) of vaccine recipient and uptake (Table 6). There was also a negative association with year study was performed, indicating a downward trend. Additionally, studies in the U.S. showed lower uptake than studies outside the U.S., while adjusting for year and age of recipient. However, neither of these results were statistically significant.

Vaccination Intention by Belief in HPV Vaccine Safety and Efficacy

There were five studies relating belief in the safety and efficacy of the HPV vaccine to intention to vaccinate. Four of these studies involved individuals' intention (Di Giuseppe et al., 2008; Hsu et al., 2009; Juntasopeepun, Suwan, Phianmongkhol, & Srisomboon, 2012; Krawczyk et al., 2012), and one study involved parental intention to vaccinate their children by belief in safety and efficacy (Baldwin, Bruce, & Tiro, 2013). There was high heterogeneity between the four studies on pooled intention (I2=91.48%) and therefore pooled estimates may not be appropriate. The one study involving parental intention showed a strong effect of belief in safety and efficacy (aOR = 2.95 [95% CI:

1.97-4.4]). All studies indicate people who believe in safety and efficacy of vaccine are more likely to intend to vaccinate or get their children vaccinated, with odds ratios ranging from 1.11 to 2.95 (Figure 10).

Vaccination Intention by Physician Recommendation

There were seven studies investigating physician recommendation as a predictor of vaccine intention. Five of these studies involved individual intention (Di Giuseppe et al., 2008; Hsu et al., 2009; Juntasopeepun et al., 2012; Krawczyk et al., 2012; Young et al., 2010), and two studies investigated how physician recommendation affected parental intention to vaccinate their child (Gottlieb et al., 2009; Hanley et al., 2012). The five studies on individual intention had low heterogeneity ($I^2 = 0.00\%$) with an amalgamated (adjusted) odds ratio for these four studies of 1.32 [95% CI: 1.23-1.41] (Figure 11). The two studies on physician recommendation and parental intention had identical odds ratios, 12.60, and the pooled confidence interval was 8.07-19.67.

Vaccination Intention by Belief in Susceptibility to HPV

A total of nine studies examined the relationship between belief in susceptibility to HPV and intention to receive the vaccine. Of these nine studies, five involved individual intention (Di Giuseppe et al., 2008; Hsu et al., 2009; Juntasopeepun et al., 2012; Kahn et al., 2008; Krawczyk et al., 2012) and four involved parental intention (Baldwin et al., 2013; Hanley et al., 2012; Hofman et al., 2014; Marlow et al., 2007). There was moderate heterogeneity between studies involving individual intention (I^2=52.21%) and the pooled estimated odds ratio was 1.20 [95% CI: 1.10-1.32] (Figures 12 and 13). However, there was high heterogeneity between studies on parental intention (I^2=88.07%) with odds ratios ranging from 1.03 to 2.30. Nevertheless, the majority of all

studies indicated a positive association between belief in susceptibility and vaccine intention and uptake, both in individuals and parents (8 of 9 ORs >1).

Vaccination Intention by Belief in Severity of HPV

There were seven studies relating belief in the severity of HPV (including progression to cervical cancer) to intention to receive HPV vaccine. Five of these studied involved individual intention (Di Giuseppe et al., 2008; Hsu et al., 2009; Juntasopeepun et al., 2012; Kahn et al., 2008; Krawczyk et al., 2012) and two involved parental intention to vaccinate their children (Baldwin et al, 2013; Hofman et al., 2014). There was high heterogeneity between the studies of individual intention (I^2=86.44%), with odds ratios ranging from 0.90 to 1.39 (Figure 14). The two studies on parental intention had contradictory findings, with one study reporting an odds ratio less than 1 (0.79 [95% CI: 0.51-1.22]) and the other with an odds ratio greater than 1 (1.22 [95% CI: 1.03-1.46]).

Discussion

Our findings show that physicians are very likely to recommend or prescribe the HPV vaccine overall, but are less likely to recommend the vaccine for younger recipients, specifically those aged less than 14 years. This runs contrary to the Advisory Committee on Immunization Practices (ACIP) recommendations for routine HPV vaccination of females aged 11 or 12 years or catch-up vaccination in women 13–26 years of age.

Physician recommendation was a strong predictor of vaccination intention. Recognizing the low heterogeneity among studies of individual intention (I^2 = 0.00%), and that all studies used in our meta-analysis showed a positive association (ORs from 1.26 to 12.60), we are confident that there is a positive association and physician recommendation does increase intention to vaccinate.

Perceived severity of HPV infection was not a strong predictor of individual or parental intention to vaccinate. However, there were significant associations between belief in efficacy of the vaccine and belief in susceptibility to HPV and individual intention to vaccinate. This has strong implications for vaccination messaging, suggesting that focusing on severity of HPV and its progression to cervical cancer is not likely to be a useful measure to increase vaccine intention as focusing on efficacy and susceptibility (e.g., high prevalence of HPV), as well as focusing on getting doctors to adopt stronger positive messaging.

Although not a primary outcome, our results show that rates are lower in the U.S. versus other countries for both intention and uptake when adjusting for the year study data were collected and age of potential recipient (Tables 4 and 6). Future studies could compare messaging and vaccination programs that prove to be successful either outside the U.S. or using positive deviance analysis to identify successful U.S. programs to bolster rates within the U.S. (Cassidy & Schlenk, 2012).

Results in Relation to a Meta-Analysis of Vaccine Acceptability among Men

In 2013, Newman, Logie, Doukas, and Asakura published a meta-analysis of 29 cross-sectional studies of vaccine acceptability among men. They calculated mean acceptability across studies (on a 100 point scale), and performed a meta-analysis on studies reporting correlates of vaccine acceptability. Among the 22 investigations reporting HPV vaccine acceptability, the mean acceptability ranged from 8.2 to 94.0 (on a scale of 0-100) with overall mean acceptability of 56.6 (SD 21.3; Newman et al.). These acceptability mean results are lower than values we found for both parental intention to vaccinate daughters and individual women's intentions to vaccinate.

Among their study's key influential correlates of HPV vaccine acceptability among men were perceived HPV vaccine effectiveness (6 studies, r= 0.19, p<0.001, I^2=58.36) and healthcare provider recommendation (5 studies, r= 0.42, p<0.01, I^2=92.13; Newman et al., 2013). Although using different measures, these results are consistent with our findings regarding perceived efficacy and physician recommendation as being strongly associated with vaccine intention in women.

Strengths and Limitations

Strengths of this study were a broad and inclusive search of the literature, independent data abstraction by three researchers with disagreements in abstracted values settled by consensus, and attention to predictors of uptake and intention to vaccinate. Further, we used subgroup analysis and meta-regression to investigate sources of heterogeneity.

There are several potential limitations. Results for uptake are limited to young women. Substantial heterogeneity between studies limited our ability to amalgamate their results. In addition, adjusted odds ratios were adjusted for a variety of variables. Subgroup analysis and meta-regression did reduce heterogeneity, but for some proportions, such as percent uptake and percent intention, ranges are preferable to overall estimates, as high heterogeneity may invalidate combined estimates.

A potential source of variation in odds ratios included in this study is that almost all papers used different sets of adjustment variables (Table 3), or *no* adjustment variables, indicating widely varying rationales in how researchers considered their statistical modeling. This is an issue of confounding bias in the reported odds ratios, in contrast to the issue addressed by meta-regression, which adjusts for an inclusion/exclusion variable, such as odds ratios calculated in different countries. One

potential method to address this is to consider a causal diagram, i.e., a directed acyclic graph (DAG), for each exposure of interest (Shrier & Platt, 2008). From these diagrams, minimally sufficient sets of adjustment variables could be identified, which would avoid confounding bias in the estimate of the odds ratio (Greenland, Robins, & Pearl, 1999). Furthermore, there may be *several* alternative sufficient sets of study variables that could be used to address bias, or, in some cases, the sufficient adjustment set is null and the crude odds ratio is suitable (Oakes & Kaufman, 2006). However, currently, protocols to address sufficiency of adjustment within the context of a meta-analysis do not exist, and it would be useful if they could be developed.

Another potential source of variation between studies of intention to vaccinate could be the different scales used to measure predictors of intention. For example, for individual belief in susceptibility and intention to vaccinate, one study used a 5-point Likert scale (Hsu et al., 2009) and another used a 10-point Likert scale (Di Giuseppe et al., 2008). However, results of meta-regression indicate no significant effect of scale on the odds ratios. Nevertheless, future studies may develop techniques to adjust for different scales of odds ratios and put amalgamated estimate on common scale where appropriate.

Conclusions

Physician recommendation is a strong predictor of vaccination intention, and physicians are more likely to recommend vaccine to older versus younger female patients. Although it does appear that parental intention to vaccinate is decreasing over time, it is too soon to draw a strong conclusion based on these studies alone. However, these findings do support the statements of the CDC (2012) that progress toward increasing HPV vaccination has stalled and physicians and care-providers need to step up

their efforts by talking to parents about the importance of HPV vaccine just as they do other vaccines. As such, CDC officials urge healthcare providers to increase the consistency and strength of their recommendation of the HPV vaccine, especially when patients are 11 or 12 years old.

At the present time, 8 years post-HPV vaccine-approval, campaigns to increase HPV vaccination uptake might better focus on physician scripting and adherence to guidelines, than on potential recipient's attitudes toward the vaccine, especially focusing on trust in safety and effectiveness over susceptibility and severity of HPV as a motivator to receive the vaccine.

Table 3. Summaries of Included Studies

Year published	Authors	Country	Study time period	Study location (geographical)	Study population	Risk of bias
2009	Blumenthal, J. et al.	USA	(unclear) Before 2009	New York	162 female aged 13 to 18 years	High
2008	Wong, L.	Malaysia	2008?	Malaysia	40 young unmarried women aged 13 to 27 years	High
2007	Gerend, M. et al.	USA	July to November 2005	North Florida	58 primarily low-income minority women aged 18 to 50	High
2009	Chan, S. et al.	China	January to June 2006	Hong Kong	250 female aged 12 to 19 years	High
2010	Kang, H. et al.	South Korea	April to June 2008	South Korea	1359 female aged 18 to 32 years	Moderate
2003	Kahn, J. et al.	USA	2002?	Cincinnati	52 female aged 18 to 30 years	Moderate
2009	Katz, M. et al.	USA	Summer of 2007	Ohio Appalachia counties	114 women aged 18 to 26 years	Moderate
2009	Podolsky, R. et al.	USA	2009	New York City and El Salvador	308 mothers of children aged 8 to 18	Moderate
2007	Duval, B. et al.	Canada	April to December 2006	Nova Scotia (NS), Quebec (PQ), Ontario (ON) and British Columbia (BC)	1282 physicians	Moderate
2008	Feemster, K et al.	USA	December 2006 to February 2007	Pennsylvania	105 pediatric clinicians	Moderate
2009	Henninger, J	New Zealand	May 2008	Christchurch, New Zealand	155 general practitioners and practice nurses	Moderate
2009	Reiter, P. et al.	USA	July to October 2007	North Carolina	889 parents of girls aged 10 to 18 years	Moderate
2013	Stocker, P. et al	Germany	Septemberto December 2010	Berlin	442 students aged 14 to 19 years	Moderate
2014	Taylor, V. et al.	USA	Nine month period during 2012 and 2013	Seattle	86 Cambodian mother with a daughter aged 9 to 17 years	Moderate
2013	Tsui, J. et al.	USA	January to November 2009	Los Angeles County	468 mothers of girls aged 9 to 18 years	Moderate
2013	Casey, B. et al.	USA	March 2008 to September 2009	Southeastern Kentucky	495 women aged 18 to 26 years	Moderate
2010	Forster, A. et al	UK	3/1/2009	South east of England	486 female aged 16 to 18 years	Moderate

Table 3. Continued

Year published	Authors	Country	Study time period	Study location (geographical)	Study population	Risk of bias
2008	Gerend, M. et al.	USA	February to March of 2007	Florida State University and Florida A&M University	124 students aged 18 to 26 years	Moderate
2011	Juraskova, I. et al.	Australia	June to August 2007	University of Sydney	159 female aged 17 to 27 years	Moderate
2009	Li, J. et al.	China	September 2005 to June 2007	geographically and socio-culturally diverse areas of China.	6024 women aged 14 to 59 years	Moderate
2010	Perkins, R. et al.	USA	June 2007 to February 2008	Massachusetts	76 parents of girls aged 11 to 18 years	Moderate
2013	Rahman, M. et al.	USA	September 2011 to February 2013	Galveston, Beaumont and Angleton, Texas	456 mothers with a child aged 9 to 17 years	Moderate
2005	Kahn, J. et al.	USA	Two-month period in 2004	USA	513 pediatricians and family physicians	Moderate
2010	Young, A. et al.	Philippines	June to July 2009	Central Visayan region, Philippines	435 women aged 18 to 52 years	Moderate
2010	Mortensen, G.	Denmark	January 2009	Denmark	749 women aged 16 to 26 years	Moderate
2010	Reiter, P. et al.	USA	2008	North Carolina	617 parents of adolescent females aged 10 to 17 years	Moderate
2006	Moreira, E et al.	Brazil	May to July 2002	Salvador City, Brazil	204 female participants aged 16 to 23 years	Moderate
2010	Cui, Y. et al.	USA	April to December 2007	Los Angeles County, CA.	2295 women aged 18 to 55 years	Moderate
2011	Kwan, T. et al.	China	July to November 2008	Hong Kong	943 adolescents girls	Moderate
2009	Watts, L. et al.	USA	August 2007 to April 2008	Massachusetts	227 Latina and non-Latina women aged 18 to 55 years	Moderate
2010	Wong, L.et al.	Malaysia	April to December 2007	Kuala Lumpur, Malaysia	650 Malaysian female students attending a public university	Moderate
2009	Marlow, L. et al.	UK	November 2006 to February 2007	England, Scotland, and Wales	332 women with a daughter aged 16 years or younger	Moderate
2010	Askelson, N. et al.	USA	2008	Rural, Midwest state	217 mothers who had daughters aged 9 to 15 years	Moderate
2013	Li, S. et al.	Hong Kong	November 2011 to January 2012.	Hong Kong	1820 female aged 18 to 27 years	Moderate
2009	Mathur, M. et al.	USA	August 2007 to February 2008	California	156 high school girls in 9th through 12th grades	Moderate

Table 3. Continued

Year published	Authors	Country	Study time period	Study location (geographical)	Study population	Risk of bias
2009	Christian, W. et al.	USA	Fall 2005	Kentucky	2169 women aged 18 years or older	Moderate
2007	Lenselink, C. et al.	Netherlands	2006	Nijmegen	356 parents of children aged 10 to 12 years	Moderate
2007	Dinh, T. et al.	Vietnam	First 3 weeks of June 2005	Da Nang, Vietnam	181 women who were the primary caregiver of a girl aged 10 to 18 years	Moderate
2010	Barnack, J. et al.	USA	Fall 2006	Nationwide	100 parents and 100 physicians	Moderate
2008	Fazekas, K. et al.	USA	April to May 2006	Person County, North Carolina	146 women	Moderate
2008	Di Giuseppe, G. et al.	Italy	March to May 2007	Campania, Italy	1341 women aged 14 to 24 years	Low
2007	Marlow, L. et al.	UK	February to June 2006	Guildford, Norfolk, Lambeth, Nottingham	680 mothers of girls aged 8 to 14 years	Low
2011	Brewer, N. et al.	USA	Summer 2007 to Fall 2008	North Carolina	650 parents of girls aged 10 to 18 years	Low
2013	Fisher, H. et al.	England	September 2008 to November 2010	South West of England	14282 young women born between September 1995 and August 1998	Low
2009	Jain, N. et al.	USA	May to August 2007	Nationwide	1102 were women aged 18 to 49 years	Low
2013	Spencer, A. et al	England	2011	North West of England	117343 girls aged 12 to 16 years	Low
2013	Steens, A. et al.	Netherlands	2011	Netherlands	337368 girls aged 13 to 16 years	Low
2012	Juntasopeepun, P.et al.	Thailand	May to August 2011	Northern region of Thailand	747 women aged 18 to 24 years	Low
2009	Hsu, Y. et al.	Taiwan	October 2007 to April 2008	5 universities in southern Taiwan	845 female undergraduates aged 17 to 36 years	Low
2008	Kahn, J. et al.	USA	October 2006 to May 2007	Cincinnati, Ohio, USA	409 female participants aged 13 to 26 years	Low
2012	Krawczyk, A. et al.	Canada	between 2009 to 2010	McGill University, Quebec, Canada	447 female undergraduates aged 18 to 43 years	Low
2007	Woodhall, S. et al.	Finland	November 2005	Tampere, Finland	397 adolescents and 727 parents	Low

Table 3. Continued

Year published	Authors	Country	Study time period	Study location (geographical)	Study population	Risk of bias
2009	Allen, J et al.	USA	February to March 2007	Massachusetts	1401 women aged 18 to 22 years	Low
2008	Jones, M. et al.	USA	4/1/2006	A northeastern university	202 women aged 18 to 32 years	Low
2009	Kwan, T. et al.	China	February to November 2007	Hong Kong	1450 ethnic Chinese women aged 18 or above	Low
2009	Gerand, M. et al	USA	January to June of 2008	Southeastern	82 parents with at least one child less than 18 years of age	Low
2008	Korfage, I. et al.	Netherlands	2007	Netherlands	1367 wonen	Low
2011	Litton, A. et al.	USA	December 2008 to April 2009	Alabama	403 female caregivers of girls aged 10 to14 years.	Low
2009	Sam, I. et al.	Malaysia	May 2007	Kuala Lumpur	362 Malaysian mothers with childeren aged 18 years or younger	Low
2007	Constantine, N. et al.	USA	Spring and Summer 2006	California	522 parents with daughters aged 18 years or younger	Low
2009	Dempsey, A. et al.	USA	January to March 2007	Michigan	52 mothers of girls aged 11 to 17 years	Low
2013	Laz,T. et al.	USA	2010	Nationwide	1892 female aged 18 to 26 years	Low
2012	Baldwin, A. et al.	USA	December 2008 to May 2010	Greater Dallas, Texas	256 mothers or female guardians of girls aged 8 to 22 years	Low
2009	Gottlieb, S et al.	USA	July to October 2007	North Carolina	889 parents or guardians of girls aged 10 to 18 years	Low
2009	Tozzi 2009	Italy	October to December 2007	Italy	807 mothers with a daughter aged 10 to 12 years	Low
2009	Bernat, D. et al.	USA	September 2006 to March 2007	Minnesota	1504 parents of children aged 5 to 18 years	Low
2006	Brabin, L. et al.	UK	March to April 2005	Manchester	317 parents of children aged 11 to 12 years	Low
2012	Hanley, S. et al.	Japan	July to September 2010	Sapporo, Japan	862 mothers of girls aged 11 to 14 years	Low

Table 3. Continued

Year published	Authors	Country	Study time period	Study location (geographical)	Study population	Risk of bias
2013	Hofman, R. et al.	Netherlands	June 2009 to November 2011	Netherlands	793 parents who had not yet made the decision to have their daughter vaccinated against HPV, but had to decide within 3–15 months when their daughters became 12 years of age.	Low
2008	Rosenthal, S. et al.	USA	April 2007 to January 2008	USA	153 mothers with daughters aged 11 to 17 years	Low
2010	Allen, J et al.	USA	September 2007 to January 2008	Nationwide	451 Parents of girls aged 9 to 17 years	Low
2009	Caskey. R. et al.	USA	November 2007	Nationwide	1011 female aged 13 to 26 years	Low
2007	Ogilvie, G. et al.	Canada	June 2006 to March 2007	Canada	2083 parents of children aged 8 to 18 years	Low
2011	Guerry, S. et al	USA	October 2007 to June 2008	California	503 parents/guardians of girls aged 11 to 18 years	Low

Table 4. Regression Coefficients for Meta-Regression of Parental Intention to Vaccinate Daughter

Variable	Coefficient	*SE*	*p*	95% *CI*
Year data collected	-0.0389	0.0206	0.0586	(-0.0792, 0.0014)
Age of intended recipient (years)	-0.0261	0.0178	0.1419	(-0.0610, 0.0087)
Study in U.S. (vs. not)	-0.1564	0.0652	0.0165*	(-0.2843, -0.0286)

Note. All effects adjusted for each other. I^2 (residual heterogeneity / unaccounted variability): 16.27%. Test for Residual Heterogeneity: QE (df = 22) = 25.3232, p-val = 0.2819.
*$p < .05$.

Table 5. Regression Coefficients for Meta-Regression of Vaccine Intention (Individual)

Variable	Coefficient	*SE*	*p*	95% *CI*
Year data collected	-0.0437	0.0172	0.0112*	(-0.0775, -0.010)
Age of intended recipient (years)	0.0034	0.0035	0.3341	(-0.004, 0.0103)
Study in U.S. (vs. not)	-0.1090	0.0616	0.0771	(-0.2298, 0.0119)

Note. I2 (residual heterogeneity / unaccounted variability): 14.29%. Test for Residual Heterogeneity: QE (*df* = 21) = 24.7432, *p*-val = 0.2585.

Table 6. Regression Coefficients for Meta-Regression of Female Vaccine Uptake

Variable	Coefficient	*SE*	*p*	95% *CI*
Year data collected	-0.0146	0.0311	0.6384	(-0.0756, 0.0463)
Age of intended recipient (years)	-0.0298	0.0178	0.0087**	(-0.052, -0.0075)
Study in U.S. (vs. not)	-0.1656	0.1093	0.1296	(-0.3798, 0.0486)

Note. 1+ doses; all effects adjusted for each other. I2 (residual heterogeneity / unaccounted variability): 81.78%. Test for Residual Heterogeneity: QE ($df = 19$) = 99.6664, p-val < .0001.

*$p < .01$.

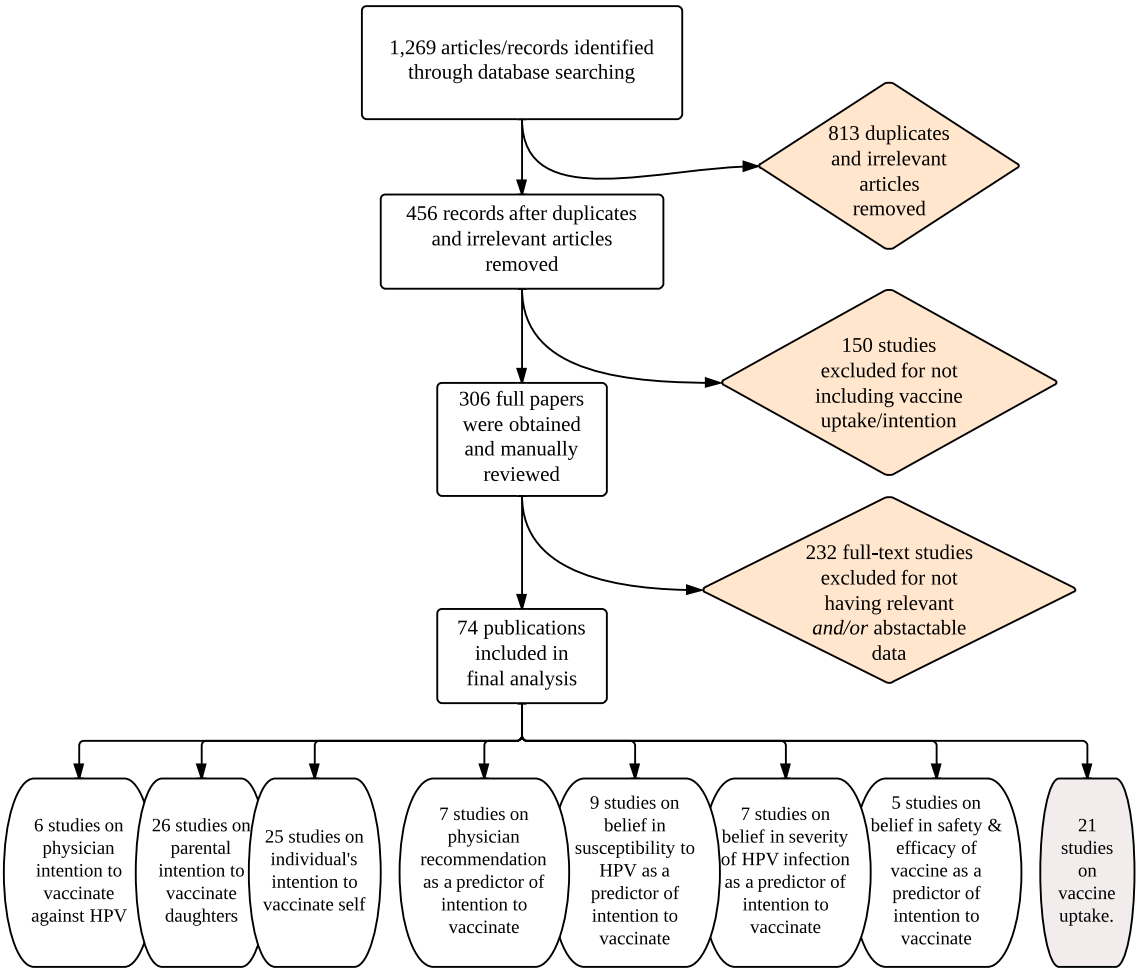

Figure 4. Attrition Diagram Showing Study Selection

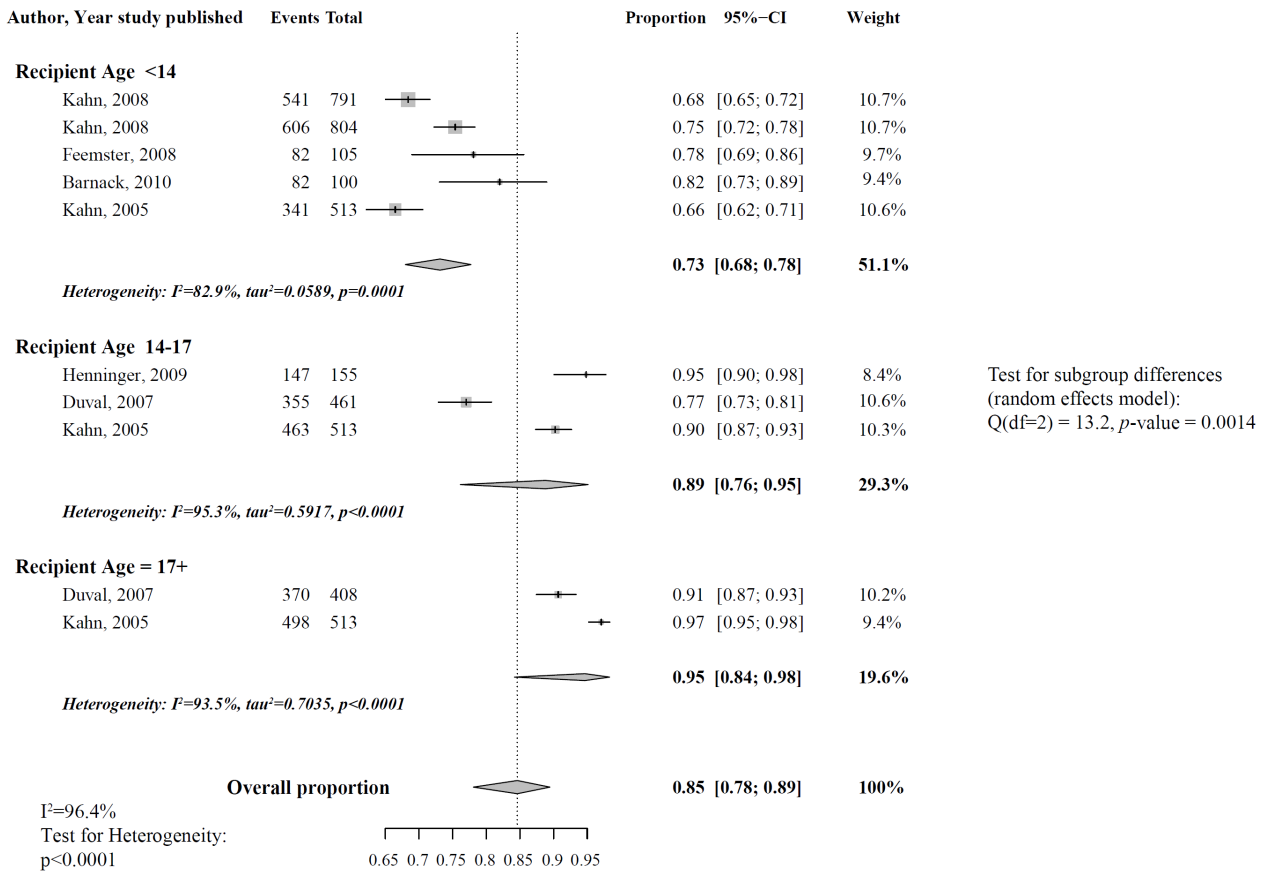

Figure 5. Meta-Analysis Forest Plot of Proportion of Physicians Who Intend to Prescribe/Recommend HPV Vaccine (by Intended Age of Recipient). Test for Subgroup Differences between Age Categories (Random Effects Model) Q ($df = 2$) = 13.2, $p = 0.0014$

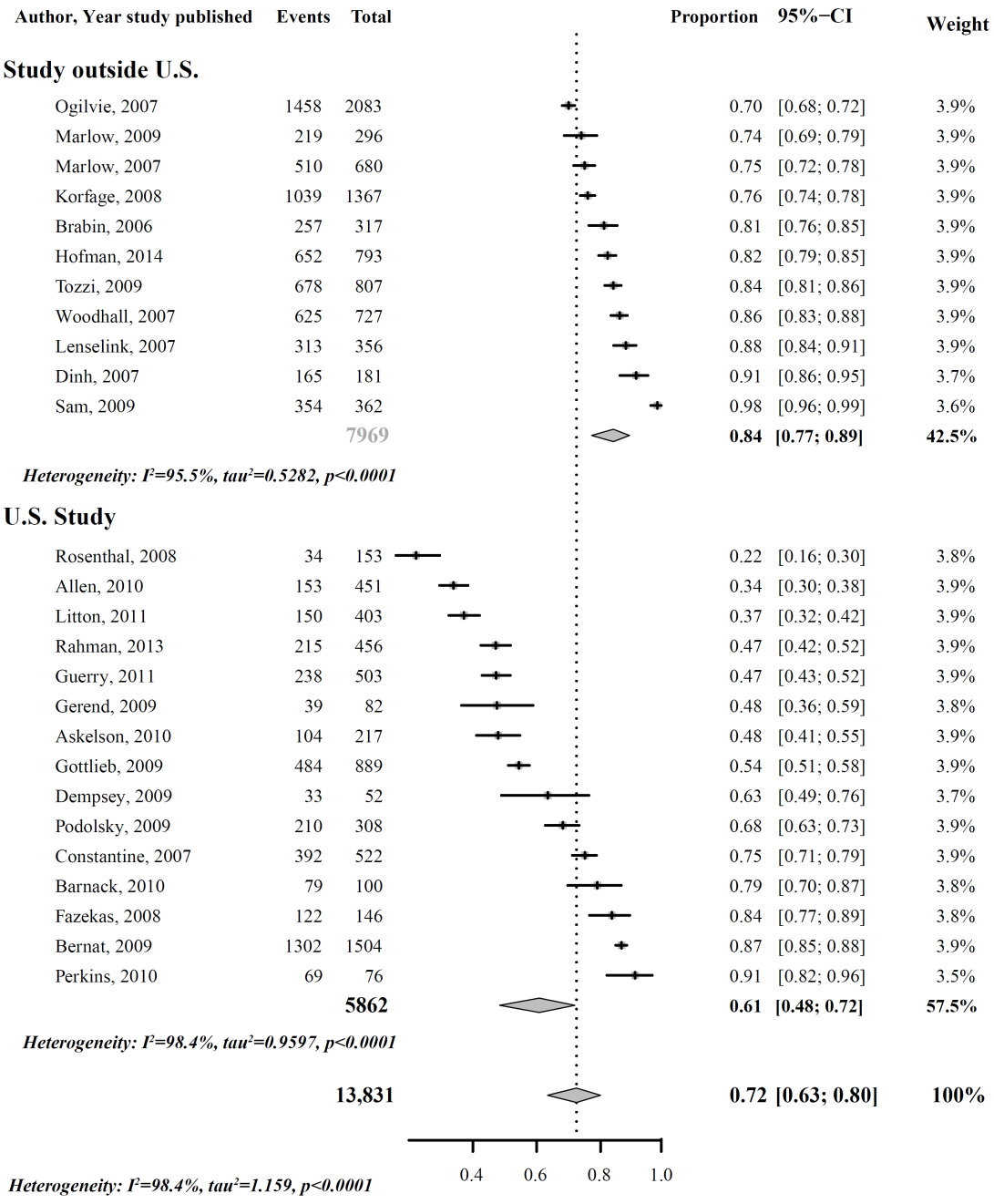

Figure 6. Meta-Analysis Forest Plot of Proportion of Parents (with 95% CI and Random-Effects Weighting Per Study) Who Intend to Have Their Daughter Receive the HPV Vaccine by Whether Study Was Conducted in U.S.

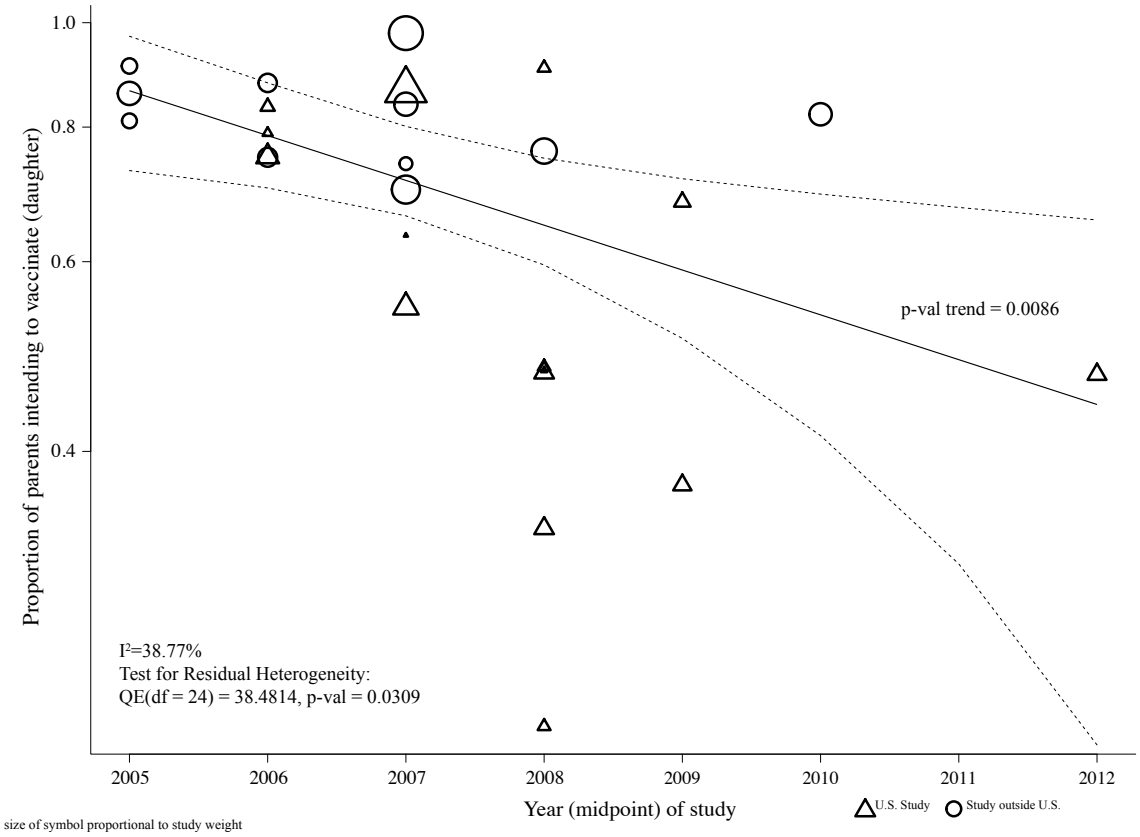

Figure 7. Meta-Regression Plot of Proportion of Parents Who Intend to Have Their Daughter Receive the HPV Vaccine by Year of Study and Whether Study Was Conducted in U.S.

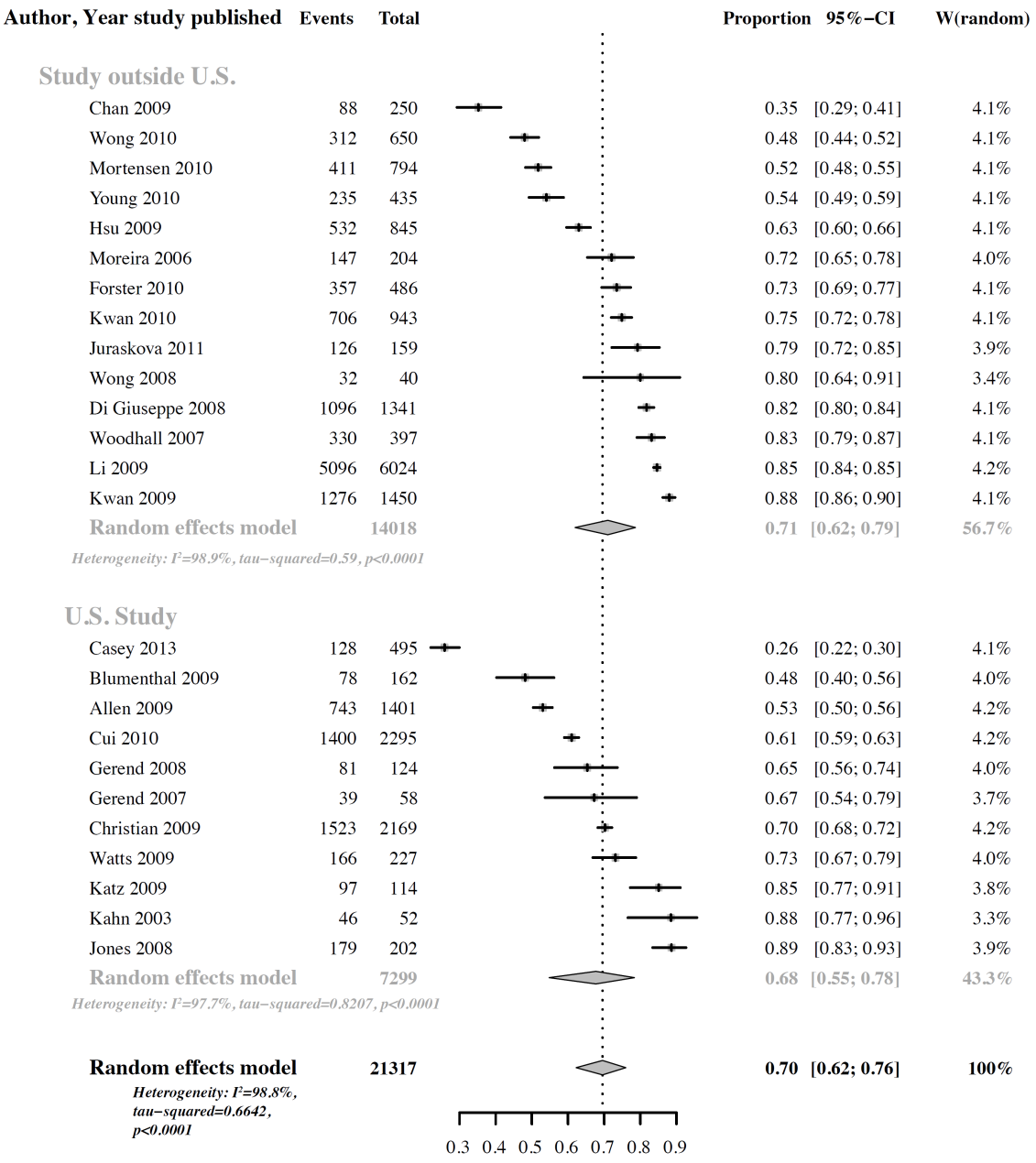

Figure 8. Meta-Analysis Forest Plot of Proportion of Individuals Who Intend to Receive The HPV Vaccine by Whether Study Was Conducted in U.S.

*$p < .05$.

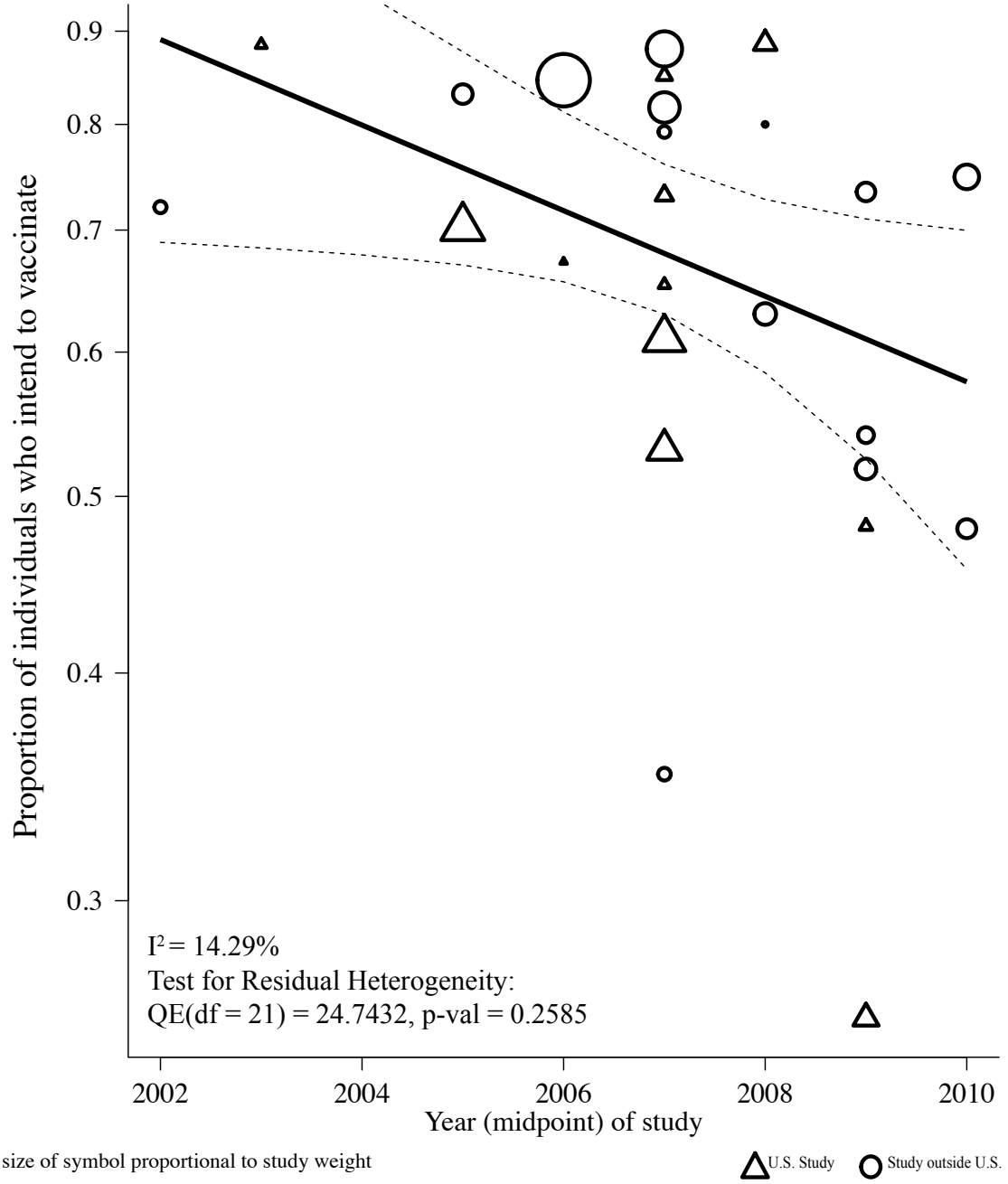

Figure 9. Meta-Regression Plot of Proportion of Individuals Who Intend to Receive the HPV Vaccine by Year and by Whether Study Was Conducted in U.S.

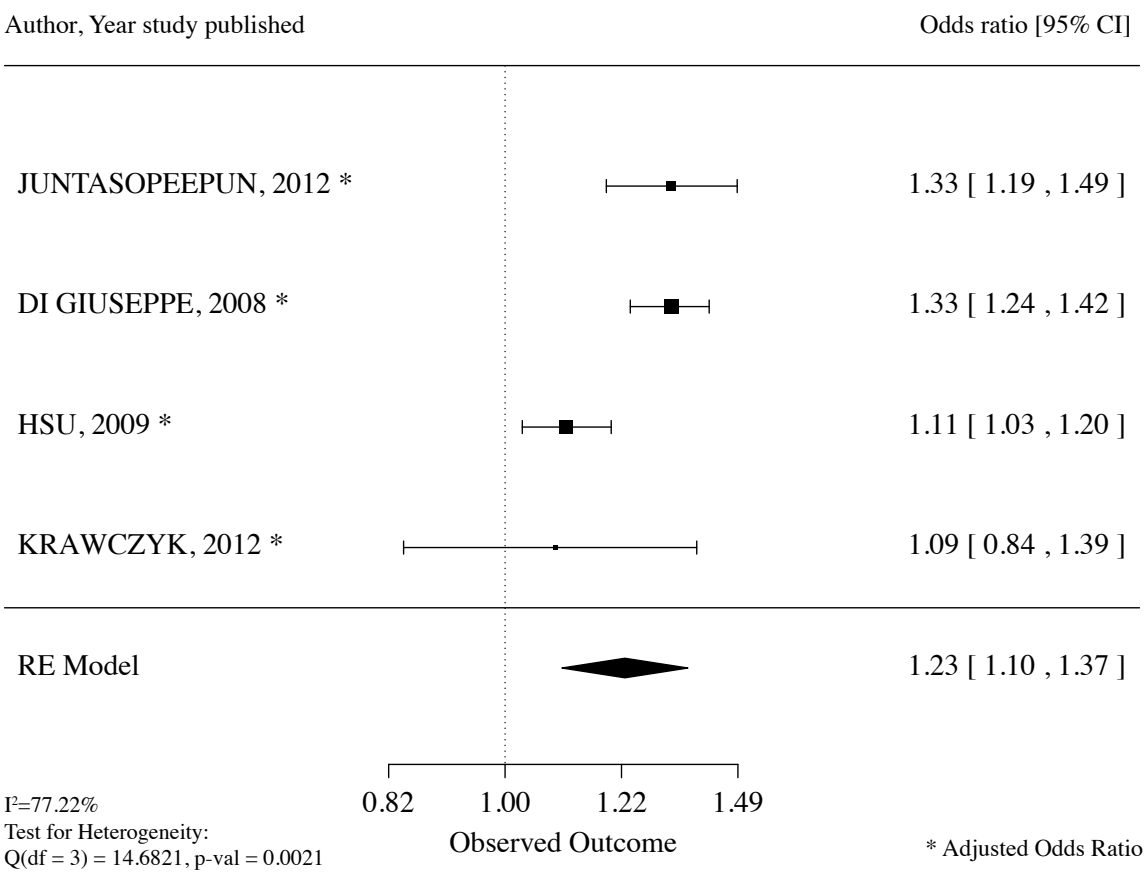

Figure 10. Meta-Analysis Forest Plot of Odds Ratios for an Individual's Belief in Vaccine Safety and Efficacy as a Factor for Vaccination Intention and Uptake for that Individual

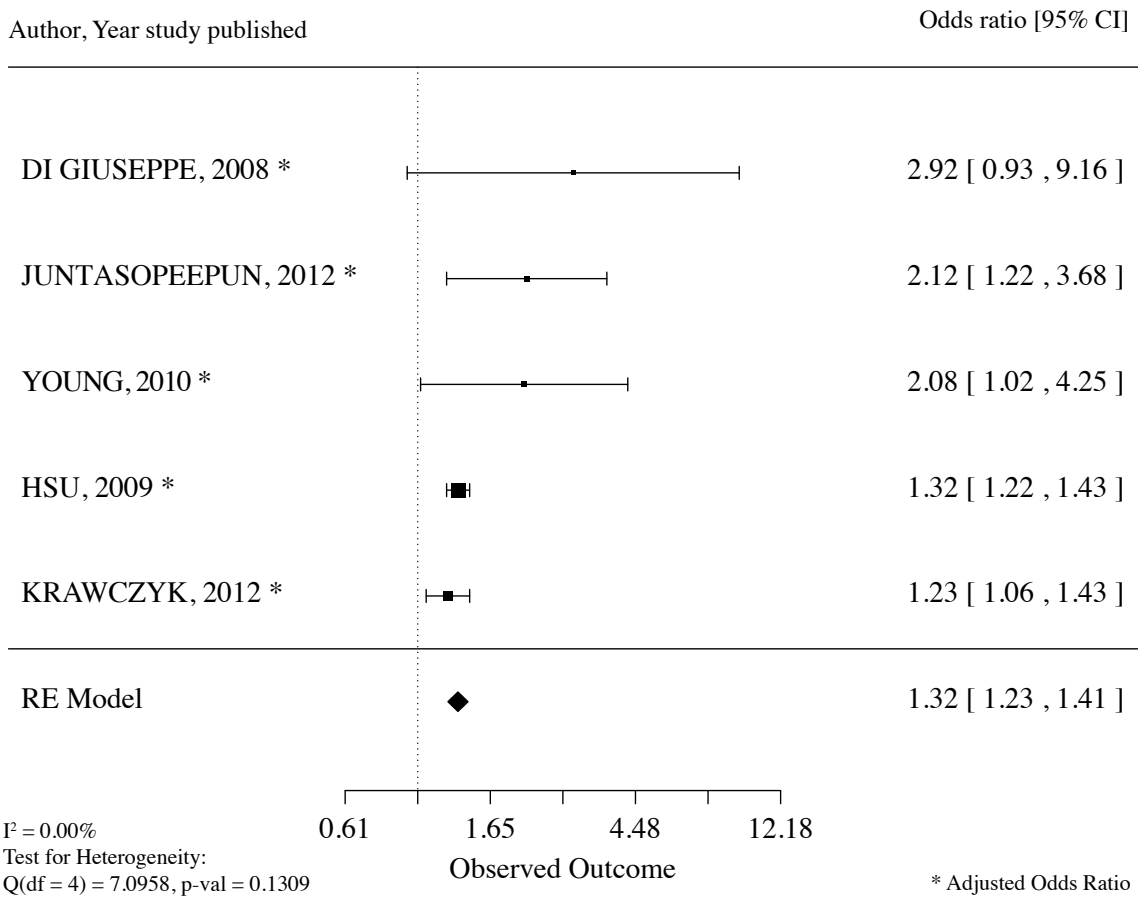

Figure 11. Meta-Analysis Forest Plot of Odds Ratios for Physician Recommendation as a Factor for Vaccination Intention and Uptake for an Individual

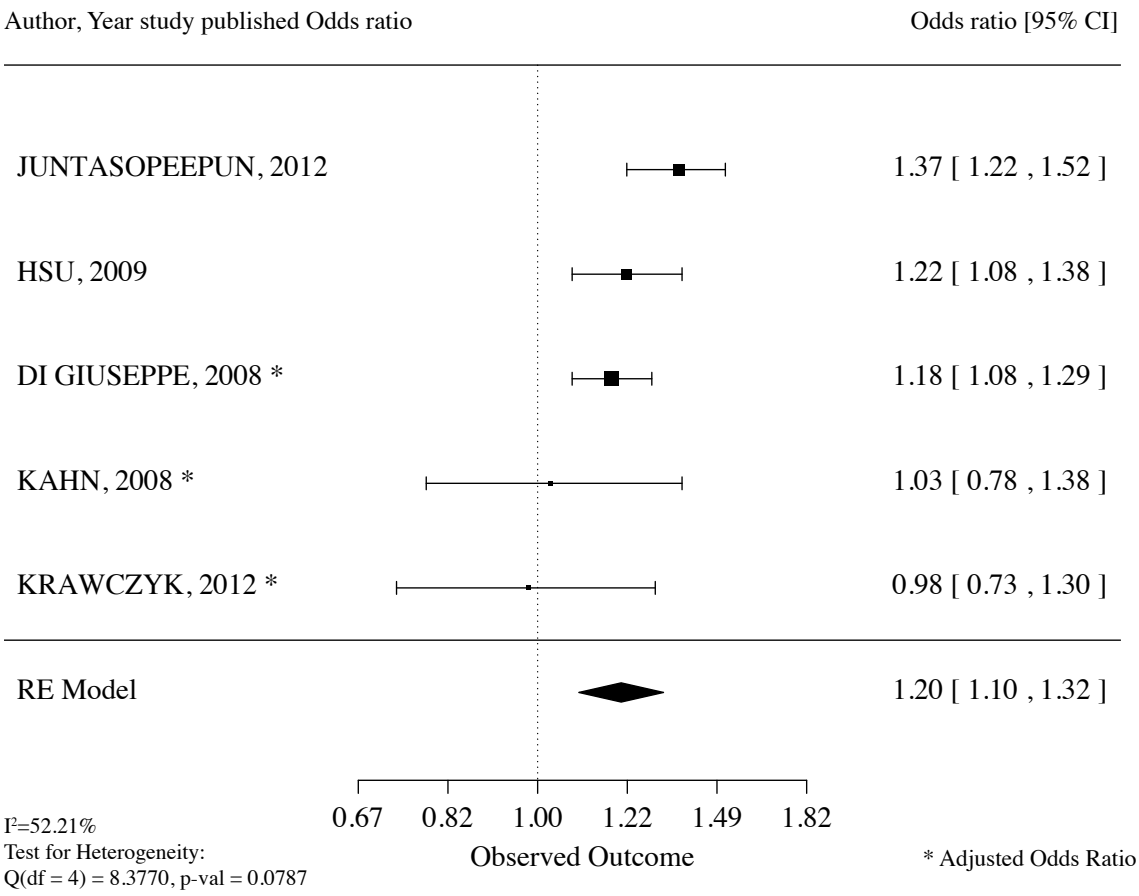

Figure 12. Meta-Analysis Forest Plot of Odds Ratios for an Individual's Belief in Susceptibility to HPV as a Factor for Vaccination Intention and Uptake for that Individual

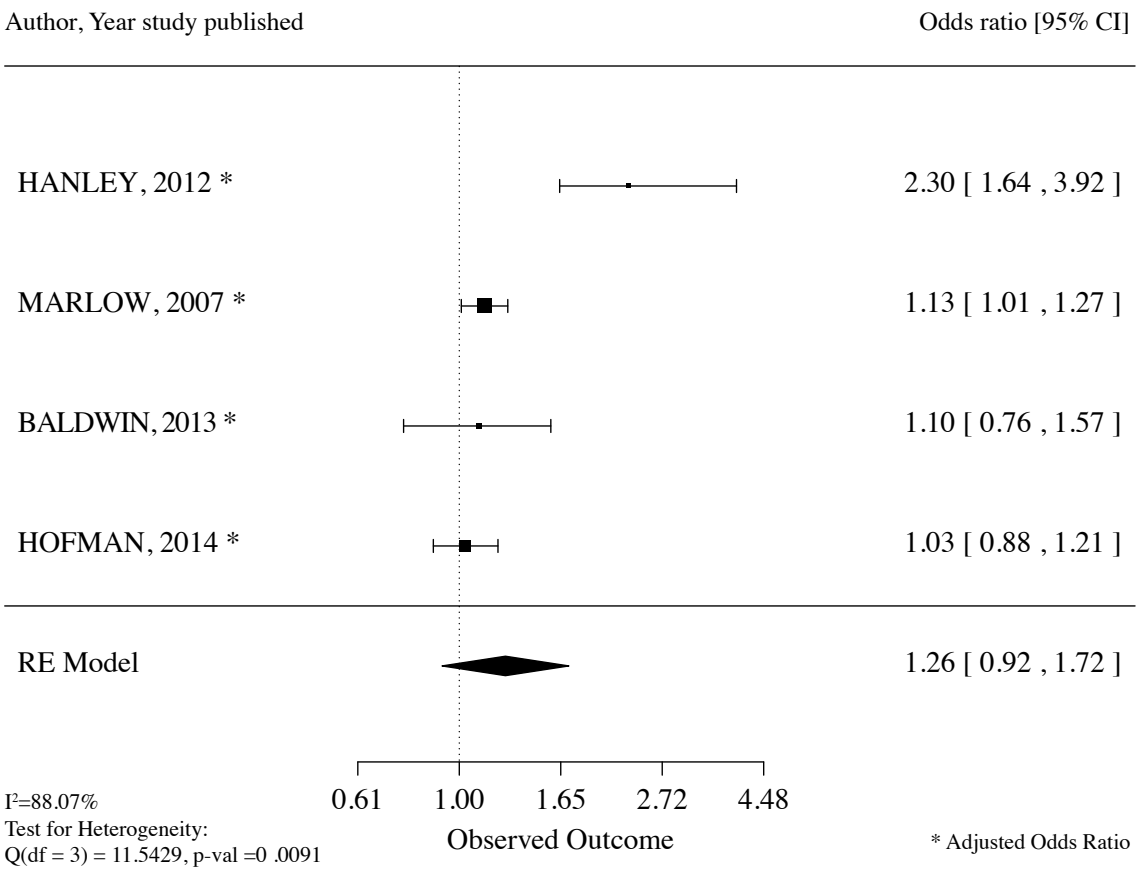

Figure 13. Meta-Analysis Forest Plot of Odds Ratios for an Individual's Belief in Susceptibility to HPV as a Factor for Parental Vaccination Intention and Uptake

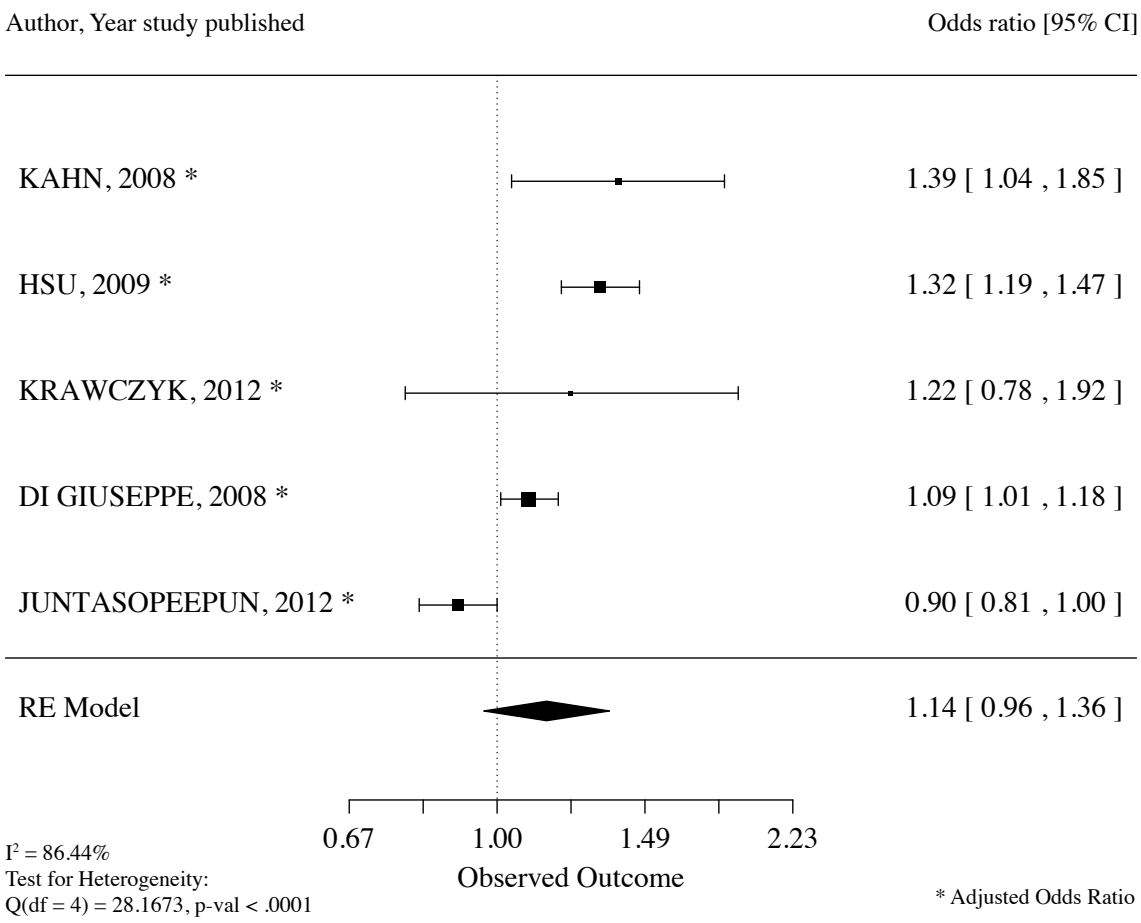

Figure 14. Meta-Analysis Forest Plot of Odds Ratios for an Individual's Belief in Severity of HPV Infection (Including Progression to Cervical Cancer) as a Factor for Vaccination Intention and Uptake for that Individual

CHAPTER 4

FACTORS RELATED TO HPV VACCINE UPTAKE AND 3-DOSE COMPLETION AMONG WOMEN IN A LOW-VACCINATION REGION OF THE USA

Abstract

Objective

The objective of this study is to assess the demographic and attitudinal factors associated with HPV vaccine initiation and completion among 18–26-year-old women in Utah.

Method

Between January 2013 and December 2013, we surveyed 325 women from the University of Utah Community Clinics about their HPV vaccine related beliefs and behaviors. Odds ratios (ORs) were estimated from logistic regression models to identify variables related to HPV vaccine initiation and series completion.

Results

Of the 325 participants, 204 (62.8%) had initiated the vaccine and 159 (48.9%) had completed the 3-dose series. The variables associated with HPV vaccine initiation were lower age (OR = 1.18 per year); being unmarried (OR = 3.62); not practicing organized religion (OR = 2.40); knowing how HPV spreads (OR = 6.29); knowing the connection between HPV and cervical cancer (OR = 3.90); a belief in the importance of

preventive vaccination (OR = 2.45 per scale unit); strength of doctor recommendation (OR = 1.86 per scale unit); and whether a doctor's recommendation was influential (OR = 1.70 per scale unit). These variables were also significantly associated with HPV vaccine completion.

Discussion

Our findings may be used to develop interventions to improve HPV vaccination rates among young women in Utah.

Introduction

The American Cancer Society estimates that in 2014, there will be over 12,000 new cases of invasive cervical cancer diagnosed in the United States and over 4,000 women will die from this disease ("What Are the . . . ," 2014). Human papillomavirus (HPV), the most common sexually transmitted infection (Centers for Disease Control and Prevention [CDC], 2014a; Satterwhite et al., 2014), has been shown to be necessary to cause cervical cancer (Bhatia et al., 2013; Lowy & Schiller, 2006; Walboomers et al., 1999). Recognition of this link led to the development of vaccines protecting against infection with certain high-risk types of HPV. There are currently two HPV vaccines available: Merck's Gardasil® vaccine (CDC, 2013b), proved highly effective in preventing the highest prevalence HPV types 16 and 18 (which cause up to 70% of all cervical cancers), as well as HPV types 6 and 11 (which cause about 90% of genital warts) [Bhatia et al., 2013; Bosch et al., 1995; CDC, 2012; Hariri et al., 2014); and GlaxoSmithKline's Cervarix® vaccine (CDC, 2013a), targeting the two most common oncogenic HPV types (16 and 18) (Bhatia et al., 2013; Hariri et al., 1995).

In 2006, the Centers for Disease Control (CDC) Advisory Committee on

Immunization Practices (ACIP) recommended a 3-dose HPV vaccination series as a routine vaccine for girls age 11–12 years old (Markowitz et al., 2007). Vaccine administration is optimal at this age because adolescents have the best immunoresponse to the vaccine and likely have not yet been exposed to the virus (Markowitz et al., 2007). However, the ACIP also recommended the HPV vaccination series as a catch-up vaccine for young women age 13–26 years old (Markowitz et al., 2007). It is hypothesized that with good vaccination coverage, the prevalence of HPV and HPV-associated cancers will decline (Barnabas et al., 2006; Lowy & Schiller, 2006; Markowitz et al., 2007; Markowitz et al., 2013).

Despite this opportunity for cervical cancer prevention, HPV vaccination rates are low in the United States. In 2013, just 57.3% of adolescents age 13–17 years old had received 1 dose of the vaccine, and only 37.6% had completed the 3-dose series (Elam-Evans et al., 2014). Coverage is especially poor in Utah, with just 44.3% of Utah adolescents initiating the vaccine, and 20.5% completing the 3-dose series (Elam-Evans et al., 2014). Most recent data indicate that uptake is the worst among young women: only 34.5% of women age 19–26 years old report receiving at least 1 dose of the HPV vaccine (Williams et al., 2014). State-specific data for this age group are unavailable. In spite of this low HPV vaccine coverage, recommendations from physicians remain suboptimal for all age groups (Vadaparampil et al., 2014).

While the choice whether or not to vaccinate adolescent usually falls to their parents, young women who are eligible to receive the vaccine are able to make the decision for themselves. These women are responsible for their *own* health, so their attitudes towards receiving the HPV vaccine and their decision-making processes may be

different from those of the parents of young adolescents. There have been many studies on women's beliefs and behaviors related to the HPV vaccine, but few studies have specifically focused on a state with low HPV vaccine initiation and completion rates (Brewer & Fazekas, 2007; Gold, Naleway, & Riedlinger, 2013; Kennedy et al., 2011; Kepka et al., 2014; Kharbanda et al., 2013; Rosenthal et al., 2011; Verdenius et al., 2013; Weiss, Rosenthall, & Zimet, 2011).

The purpose of this study is to assess the demographic and attitudinal factors associated with HPV initiation and completion among 18- to 26-year-old women in Utah. Our goal is to generate information to develop intervention programs to increase HPV vaccination in this age group in Utah.

Methods

This study was approved by the University of Utah Institutional Review Board.

Survey Creation

Previous studies have used Health Belief Model (HBM) constructs (Donadiki et al., 2014; Reiter et al., 2009) and/or Social Cognitive Model (SCM) factors (Chan et al., 2009) to identify predictors of HPV vaccination intention. The HBM considers potential motivating factors such as perceived severity (an individual's assessment of the seriousness of the condition), perceived susceptibility (an individual's assessment of their risk of getting the condition), expected benefit (an individual's assessment of the positive rewards of adopting the behavior), self-efficacy, and perceived barriers (Bandura, 1997). Each question included in our survey corresponded to a conceptual variable representing one facet in either HBM or SCM (Bandura, 1997, 2001). Survey items were also motivated by use of directed acyclic graphs and a survey developed by other researchers

and shared with permission (Greenland, Pearl, & Robins, 1999; Rosenthal et al., 2011).

Our study questionnaire included six sections:

1. Attitudes about health,
2. Attitudes about vaccines,
3. Demographic information and history/family history of cancer,
4. Attitudes about reproductive health,
5. Attitudes about the HPV vaccine, and
6. Future (intended) HPV vaccine use.

Data Collection

We recruited participants from the University of Utah Community Clinics through the University of Utah Primary Care Research Network. An initial data query of potential participants was performed to identify young women age 18–26 years old who had a University of Utah Community Clinic visit in the 12 months preceding the query. Two groups of 1,000 were created. In the first group, we included 336 women who had at least one documented dose of the HPV vaccine and 664 unvaccinated women. In the second group, we included 233 who had initiated the vaccine and 776 unvaccinated women. Potential participants were sorted by zip code and only those within the catchment areas for the University of Utah Community Clinics were included in the sample. Potential participants were mailed a letter briefly describing the project and given the opportunity to opt out. Remaining participants were mailed a letter describing the project in greater detail, a paper version of the survey, and a business reply envelope to return the survey.

Introduction letters with study opt-out information went out in two waves of 1,000. The initial wave of 1,000 opt-out letters was sent out in January 2013. After

excluding nine opt-outs, we had a response rate of 84 of 991 surveys (8.5%). The target response rate for analysis was between 300–325 completed surveys. In order to improve return rates, the implementation protocol was revised, following the Tailored Design Method proposed by Dillman, Smyth, and Christian (2009). Modifications to the survey wave, according to the Dillman method, included:

- 1,000 opt-out letters and cover letters were printed in high-resolution color and hand-signed,
- Surveys now included a 5$ bill thank you with return envelope, and
- Address verification services were used.

These revisions bolstered returns from 8.5% to over 27.1% (244 surveys completed of 901 delivered). All surveys were mailed between January and December 2013.

Data Analysis

Fisher's Exact Tests and Logistic Regression were used to determine differences in demographics, initiation, and completion rates between the two waves of survey responses to assess appropriateness of pooling results. Summary statistics for participant characteristics were calculated by vaccination status. Principal component factor analysis with promax rotation was used for the attitude questions to derive useful attitude factor variables. Correlation between items in factor variables was assessed using Cronbach's alpha (Table 7).

A Directed Acyclic Graph (DAG) (Figure 15) was created to help identify and adjust for potential confounders and minimize bias assessing individual predictors of vaccine initiation (1+ dose) and series completion (3 doses; Evans et al., 2012; Shrier &

Platt, 2008). An online tool, DAGitty (http://www.dagitty.net), was used to produce potential DAGs and derive minimally sufficient adjustment sets for predictor variables (Textor, Hardt, & Knuppel, 2011). Univariate and multivariate logistic regression models were used to calculate odds ratios (ORs) to identify variables related to vaccine initiation and series completion.

Factor and Principal Component Analysis was performed using R (R Core Team, 2013). Descriptive statistics and univariate and multivariate logistic regression was performed using SAS software, Version 9.4 of the SAS System Copyright © 2013 SAS Institute Inc., Cary, NC, USA. Results were considered statistically significant if $p<0.05$.

Results

A total of 84 of 993 surveys (8.5%) from the first wave and 244 of 901 surveys (27.1%) from the second wave were returned for a total of 328 of 1,983 returned (16.5%). Three participants were excluded: 2 for having an age out of range and 1 for incompleteness of the questionnaire. The remaining 325 were included in the final analysis. There were no statistically significant differences in age (p=0.1286), race (p=0.9336), marital status (p=0.3268), education (p=0.3135), initiation of the vaccine series (p=0.6935), or completion of vaccine series (p=0.3756) between the participants in the two survey waves, so the two waves were pooled for the analysis.

Of these 325 participants, 204 (62.8%) had initiated the vaccine series and 159 (48.9%) had completed the 3-dose series. Of the 45 who had initiated, but not completed the vaccine series, 31 (70.5%) said they intended to complete the series and 13 (29.6%) said they did not (*1 missing*). The mean age for those who initiated the vaccine was 22.4 years (s.d. 2.4 years), for those who completed the 3-dose series was 22.4 years (s.d. 2.4

years), and for those who did not receive any vaccine doses was 23.3 years (s.d. 2.3 years). Participant characteristics are presented in Table 8 and participants' HPV vaccine-related knowledge and attitudes are presented in Table 9.

The factor analysis produced a total of seven attitude factors with good interitem correlation. As explained in Table 7, the factors produced were:

1. Attitudes toward vaccines [Cronbach's alpha: 0.902],
2. Regular gynecological care [Cronbach's alpha: 0.855],
3. Comfort with sexual health (care) [Cronbach's alpha: 0.753],
4. External locus of health control 1: (medical professionals drive health) [Cronbach's alpha: 0.722],
5. Internal locus of health control [Cronbach's alpha: 0.735],
6. External locus of health control 2: (health matter of luck) [Cronbach's alpha: 0.644], and
7. Comfort with shots [Cronbach's alpha: 0.729].

Table 10 shows the significant univariate predictors of vaccine *initiation* were lower age vs. older age: OR = 1.18 per lower year [95% CI: 1.07 – 1.30]; marital status (being unmarried vs. married): OR = 3.62 [95% CI: 2.18– 5.99]; not practicing vs. practicing organized religion: OR = 2.4 [95% CI: 1.49 – 4.0]; knowledge of HPV transmission: OR = 6.29 [95% CI: 3.46 - 11.44]; known connection between HPV and cervical cancer: OR = 3.90 [95% CI: 2.21 - 6.89]; known importance of vaccine (to help prevent cervical cancer): OR = 2.45 [95% CI: 1.79 - 3.36]; strength of doctor recommendation: OR = 1.86 per Likert scale unit [95% CI: 1.27 - 2.70]; and a binary indicator of whether a physician's recommendation is influential: OR = 1.70 [95% CI: 1.38 - 2.09]. These

variables were all also significant predictors of *completion* of the 3-dose series (see Table 10). Minimal sufficient adjustment sets were derived from application of the DAG (see Figure 15) to produce subsets of variables adequate to control for potential confounding. These subsets were used to produce adjusted estimates (see Table 10).

The main reasons for not intending to initiate or complete the vaccine were waiting for more information/vaccine too new (*n*=38), married or monogamous relationship (*n*=36), cost of vaccine or unsure if insurance covers vaccine (*n*=23), concern of side effects (*n*=18), not sexually active (*n*=14), and vaccine inconvenience (*n*=7) (see Figure 16).

Discussion

The HPV vaccine has been available in the United States for 8 years, yet only one third of adolescents have been fully immunized with all 3 recommended doses, and only one third of older eligible women (age 18–26 years old) have received just 1 dose of the 3-dose series (Elam-Evans et al., 2014; Markowitz et al., 2007; Williams et al., 2014). HPV vaccine coverage varies substantially among states, with Utah having some of the lowest coverage rates in the U.S. (Elam-Evans et al., 2014). Clearly, the Unites States is far from the Healthy People 2020 target of 80% HPV vaccine coverage among eligible females, indicating an urgent need for interventions (Elam-Evans et al., 2014).

Resources are currently available to help increase HPV vaccination in Utah. In April 2007, Jon Huntsman, Sr. donated $1 million to the Utah Department of Health to educate Utahans about cervical cancer and provide low-cost HPV vaccines to eligible women (Collins & Welling, 2007). An additional $25,000 allocated by the Utah legislature was used for a public awareness media campaign and to inform physicians and

other healthcare professionals about the HPV vaccine (Collins & Welling, 2007). Additionally, the HPV vaccine is available for free or at low cost for girls age 9–18 years old through the Vaccines for Children Program and may be available for free or at low cost for women age 19–26 years old who have no insurance or insurance that does not pay for the vaccine thanks to Vaccine Patient Assistance Programs (CDC, 2014b). The results of our study can help to focus these funds and resources to reach women who have not yet initiated and/or completed the HPV vaccination series.

Our study of young women age 18–26 years old found several correlates of vaccine initiation and completion that may be useful for future public health interventions for this population. Among these correlates were lower age, awareness of HPV transmission, knowledge of its connection to cervical cancer, belief in the importance of the HPV vaccine, and a physician recommendation (especially a strong recommendation). Marital status (being unmarried), practicing organized religion, and higher education were also significant predictors of vaccine initiation and completion. Cost, being in a monogamous relationship, and novelty of the vaccine were the main barriers against vaccination.

These findings echo previous studies that identified knowledge-attitude-practice gaps in the context of the HPV vaccine (Cohen & Head, 2013). The differences we found between vaccinated women and unvaccinated women regarding risk beliefs (i.e., the vaccine is not personally relevant because they are in a monogamous relationship and the vaccine is too new and more information is needed) help explain why increasing uptake of the HPV vaccine requires targeted risk communication strategies (Cohen & Head, 2013. Additionally, our study confirms one of the most ubiquitous finding in HPV

vaccine research: the importance of a consistent and strong recommendation of the HPV vaccine from healthcare providers (Darden & Jacobson, 2014; Krawczyk et al., 2012; Rosenthal et al., 2011). However, our findings run counter to an earlier study showing no association between marital status in their multivariate analysis (Rosenthal et al., 2011). This difference could be due to the particular interplay between marriage, age, and religiosity in the state of Utah.

There are limitations to the generalizability of the current study. The majority of participants were White/Caucasian (>80%), had access to healthcare, and response rates were higher in the vaccinated vs. the unvaccinated, which may have introduced unmeasured response bias. Furthermore, cross-sectional study design prohibits assessment of causal relationships.

Conclusions

The implications of these findings may help inform policies regarding HPV vaccination education among young women. For example, without this information, programs might focus on awareness (Collins & Welling, 2007; Cui et al., 2010; Gerend & Magloire, 2008; Jain et al., 2009), but the results of this study illustrate that the significance of awareness of HPV as a predictor of vaccine uptake has diminished over time and that programs should now focus on other variables (for example, strong and consistent physician recommendations). Additionally, our findings indicate the need for discussions of risk assessment tailored to the young adult population since young women are sure of their sexual behavior in a way parents may not be of their children's. These interventions may use our results to take into account a patient's education, religious affiliation, and relationship status when having such conversations. Future research is

needed to assess the impact these tailored interventions would have on bolstering HPV vaccination rates in the low vaccination state of Utah.

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Table 7. Factor Analysis Results (Utah, January–December 2013)

Factor	Survey questions
1: Attitudes toward vaccines. [Cronbach's alpha: 0.903 (*95% CI: (0.880, 0.925))]*	• Vaccines are a good way to protect public health. • I do not like the idea of vaccines.[a] • Vaccines are generally safe. • Vaccines are a way to take good care of myself now and in the future. • Vaccines are effective. • Vaccines are safe. In particular, HPV vaccine is safe.
2: Regular gynecological care. [Cronbach's alpha: 0.856 *(95% CI: (0.819, 0.892))*]	• Gynecological/pelvic exams are necessary to stay healthy. • I get a Pap test/Pap smear according to my doctor's/health care provider's advice. • It is very important to have an annual pelvic exam.
3: Comfort with sexual health (care). [Cronbach's alpha: 0.754 *(95% CI: (0.701, 0.807))*]	• I am comfortable discussing sexual health issues with a doctor or nurse. • I am comfortable discussing sexual health issues with others such as family or friends. • I don't mind getting a gynecological/pelvic exam.
4: External locus of health control 1: (medical professionals drive health). [Cronbach's alpha: 0.720 *(95% CI: (0.668, 0.772))*]	• Having regular contact with my physician is the best way for me to avoid illness. • Whenever I don't feel well, I should consult a medically trained professional. • Health professionals control my health. • Regarding my health, I can only do what my doctor tells me to do.
5: Internal locus of health control. [Cronbach's alpha: 0.734 *(95% CI: (0.680, 0.788))*]	• I am in control of my health. • The main thing which affects my health is what I myself do. • If I take care of myself, I can avoid illness. • If I take the right actions, I can stay healthy.
6: External locus of health control 2: (health matter of luck). [Cronbach's alpha: 0.646 *(95% CI: (0.570, 0.722))]*	• Luck plays a big part in determining how soon I will recover from an illness. • My good health is largely a matter of good fortune. • If it's meant to be, I will stay healthy
7: Comfort with shots. [Cronbach's alpha: 0.729 *(95% CI: (0.660, 0.797))*]	• I am not afraid of shots. • Shots are very painful.[a]

[a] Reverse coded (6 minus response)

Table 8. Characteristic of Study Participants (Utah, January–December 2013)

	No doses (n = 121) n (%)	1+ dose (n = 204) n (%)	3 dose completion (n = 159) n (%)
Age			
18 - 21.5 y.o.	28 (23.14)	82 (40.20)	65 (40.88)
22 - 24 y.o.	48 (39.67)	70 (34.31)	53 (33.33)
24.5 - 26 y.o.	45 (37.19)	52 (25.49)	41 (25.79)
Race/ethnicity			
Asian	9 (7.44)	8 (3.92)	8 (5.03)
Black or African American	2 (1.65)	4 (1.96)	3 (1.89)
Hispanic or Latina	9 (7.44)	15 (7.35)	10 (6.29)
White/Caucasian	96 (79.34)	167 (81.86)	133 (83.65)
Other	5 (4.13)	10 (4.90)	5 (3.14)
Highest level of education			
Up to or graduated high school	24 (19.83)	25 (12.25)	17 (10.69)
Some college, but no degree	39 (32.23)	90 (44.12)	72 (45.28)
College degree	46 (38.02)	77 (37.75)	60 (37.74)
Graduate school	12 (9.92)	12 (5.88)	10 (6.29)
Marital status			
Single, never married	66 (54.55)	165 (80.88)	132 (83.02)
(Ever) Married	54 (44.63)	38 (18.63)	26 (16.35)
Ever received a cancer diagnosis			
Yes	3 (2.48)	3 (1.47)	2 (1.26)
No	118 (97.52)	199 (97.55)	155 (97.48)
Know anyone who has had a cancer diagnosis			
Yes	95 (79.51)	178 (87.25)	140 (88.05)
No	26 (21.49)	26 (12.75)	19 (11.95)
Know anyone who has had cervical cancer			
Yes	9 (9.57)	24 (13.04)	18 (12.59)
No	85 (90.43)	160 (86.96)	125 (87.41)
Practice organized religion			
Yes	72 (59.50)	75 (36.95)	53 (33.54)
No	49 (40.50)	128 (63.05)	105 (66.46)
Religion guide your daily decisions			
Yes	57 (65.52)	51 (48.57)	38 (48.10)
No	30 (34.48)	54 (51.43)	41 (51.90)

Table 9. Participants' Attitudes about and Knowledge Relating to the HPV Vaccine (Utah, January–December 2013)

	No doses (*n* = 119) *n* (%)	1+ dose (*n* = 202) *n* (%)	3 dose completion (*n* = 157) *n* (%)
Have you ever heard of human papillomavirus (HPV)?			
Yes	105 (86.78)	200 (98.04)	155 (97.48)
No	16 (13.22)	4 (1.96)	4 (2.52)
Do you know how HPV is spread?			
Yes	72 (59.50)	185 (90.69)	144 (90.57)
No	49 (40.50)	19 (9.31)	15 (9.43)
Have you ever heard of a relationship between HPV and cervical cancer?			
Yes	78 (65.00)	180 (88.24)	143 (89.94)
No	42 (35.00)	24 (11.76)	16 (10.06)
Have you ever heard of a vaccine to prevent HPV (e.g., Gardasil® or Cervarix®)?			
Yes	90 (75.00)	203 (100)	158 (100)
No	30 (25.00)	0 (0)	0 (0)
(If heard of vaccine) how important do you think the vaccine to help prevent cervical cancer is for you?			
Not at all important	10 (11.11)	5 (2.45)	2 (1.26)
Not very important	18 (20.00)	6 (2.94)	0 (0)
Somewhat important	27 (30.00)	50 (24.51)	33 (20.75)
Very important	35 (38.89)	143 (70.10)	124 (77.99)
Have you discussed the vaccine to help prevent cervical cancer with a doctor?			
Yes	34 (37.36)	201 (98.53)	158 (99.37)
No	57 (62.64)	3 (1.47)	1 (0.63)
Did a doctor recommend that you get the vaccine to help prevent cervical cancer?			
Yes	22 (55.00)	199 (98.03)	157 (99.37)
No	18 (45.00)	4 (1.97)	1 (0.63)

Table 10. Crude and Adjusted Odds Ratios (95% CIs) for Predictors of Vaccination Initiation and Completion and Adjustment Variables Used in Regression Modeling (Utah, January–December 2013)

	Initiated		Completed		
	Crude (95% CI)	Adjusted (95% CI)	Crude (95% CI)	Adjusted (95% CI)	DAG-directed Adjustment Variables
Physician rec. influential (Likert)	1.71 (1.39 - 2.11)	1.86 (1.46 - 2.36)	1.85 (1.46 - 2.34)	2.01 (1.53 - 2.63)	Factor 1: Attitudes toward vaccines, Age
Age (per year)	0.85 (0.77 - 0.94)	0.87 (0.77 - 1.00)	0.87 (0.79 - 0.95)	0.88 (0.77 - 0.99)	Education level, Factor 2: Regular Gynecological care, Factor 4: External locus of health control 1: (medical pros), Factor 5: Internal locus of health control, Marital status
Education (ref: High school)					Age
Some college	2.22 (1.13 - 4.35)	2.33 (1.15 - 4.70)	2.38 (1.20 - 4.71)	2.53 (1.25 -5.14)	
College graduate	1.61 (0.82 - 3.14)	2.72 (1.26 - 5.88)	1.79 (0.90 - 3.56)	3.07 (1.39 - 6.77)	
Graduate school	0.96 (0.36 - 2.55)	1.62 (0.55 - 4.76)	1.34 0.49 - 3.66)	2.26 (0.74 - 6.90)	
Ethnicity (White vs. non-White)	1.18 (0.67 - 2.07)	1.10 (0.60 - 2.00)	1.42 (0.81 - 2.49)	1.30 (0.72 - 2.34)	Education level, Age
Marital status (ever vs never married)	0.28 (0.17 - 0.47)	0.31 (0.18 - 0.53)	0.30 (0.18 - 0.50)	0.32 (0.18 - 0.56)	Age, Factor 2: Regular Gynecological care, Factor 4: External locus of health control 1: (medical pros), Factor 5: Internal locus of health control
Practice Organized Religion (yes vs no)	0.40 (0.25 -0.63)	0.41 (0.25 - 0.67)	0.38 (0.25 - 0.61)	0.40 (0.25 - 0.64)	Factor 1: Attitudes toward vaccines, Physician recommendation

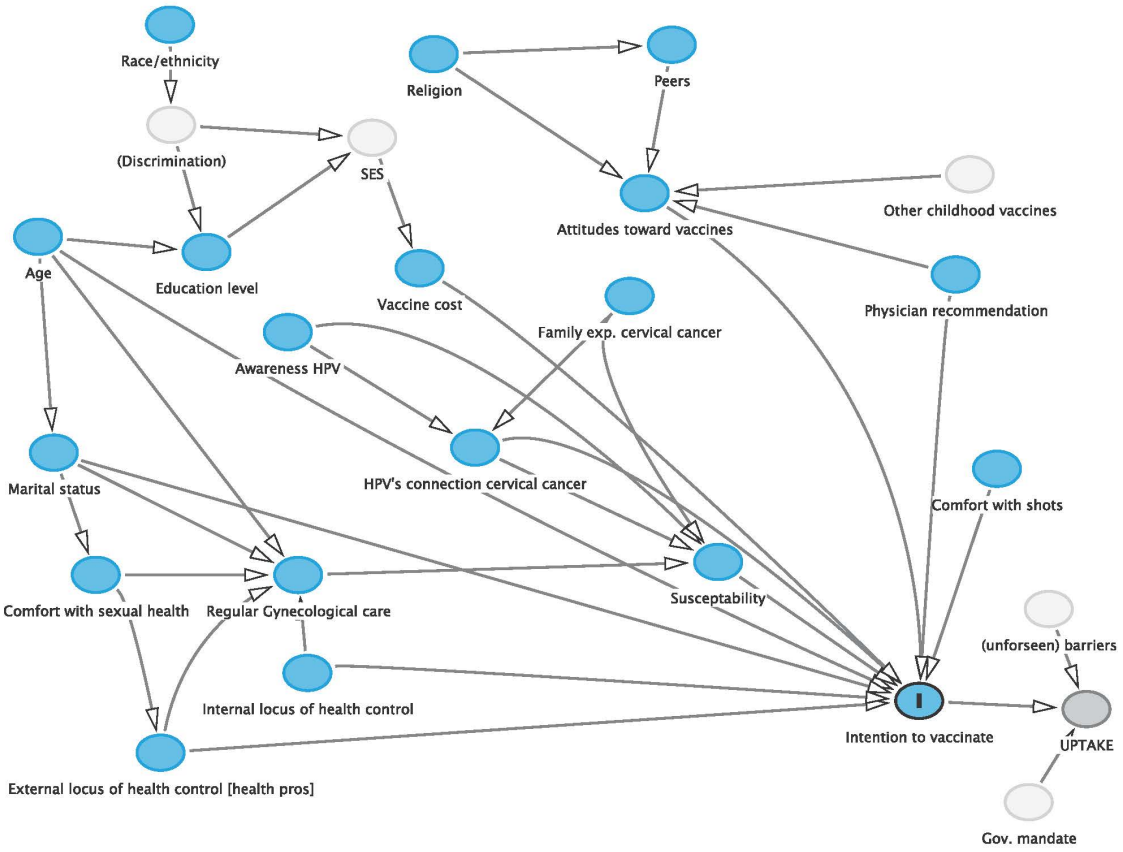

Figure 15. Potential Confounders of Predictors of HPV Vaccine Initiation and Completion (Utah, January–December, 2013)

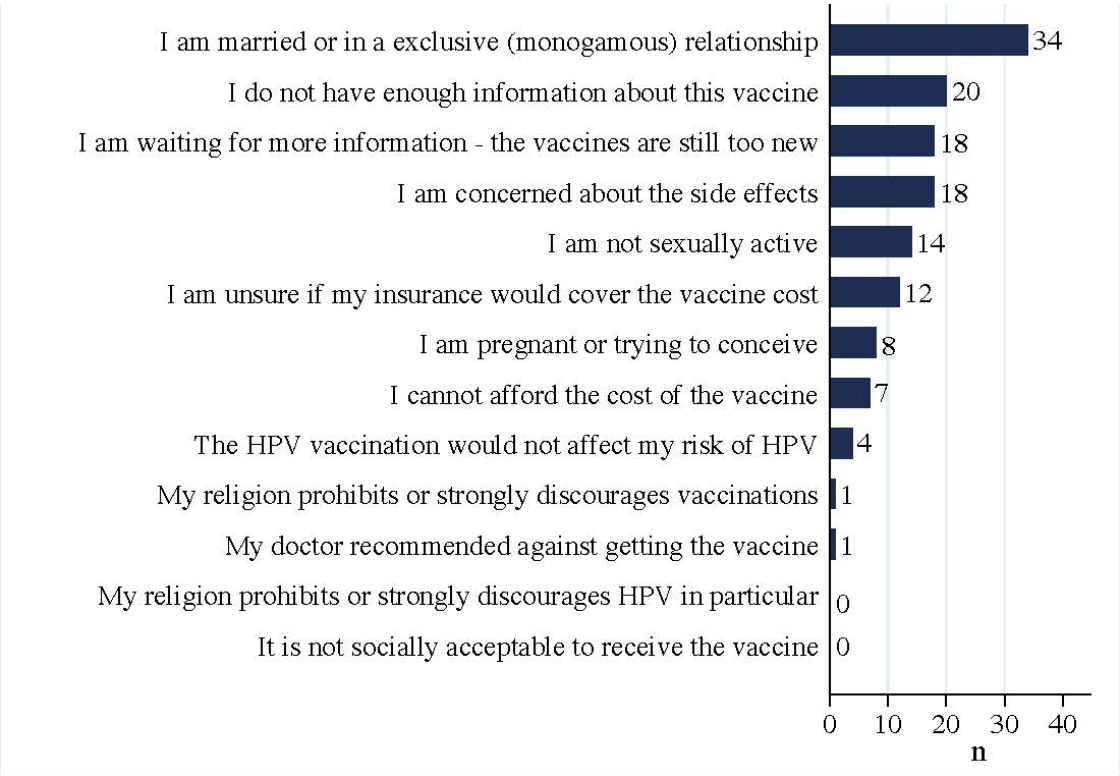

Figure 16. Reasons for Not Initiating or Completing the HPV Vaccine (Utah, January–December, 2013)

CHAPTER 5

SUMMARY

The data from study one indicate that the overall positivity of HPV is declining, especially in young women; however, the rate at which positivity is declining is slower than other studies indicate in certain age categories (Markowitz et al., 2013). Additionally, these rates of decline are slower than expected by mathematical models given adequate vaccine coverage (Barnabas et al., 2006). These results indicate a need for improved vaccination rates and, subsequently, the need for evidence-driven programs aimed to improve these vaccination rates. Furthermore, our initial study demonstrates the potential for using HPV test data from large national reference laboratories to supplement the ongoing and planned efforts to monitor HPV vaccine impact in the US (Markowitz et al., 2010).

To inform these vaccine programs, and the goal of study two, the meta-analysis of published research identified potential factors that may influence both intention to recommend the HPV vaccine, and intention to receive the vaccinate. One of the more compelling findings, and one that further drives the need for future interventions, is that individual intention to receive the vaccine is not increasing over time, and may, in fact, be decreasing over time. The remainder of study two identifies factors that may be pivotal to increase vaccination rates—both in physician intention to vaccinate, and individual and parental intention to receive vaccine.

One of these potential factors driving physician intention to prescribe the vaccine was age of intended recipient. Although the proportion of physicians who intended to recommend the HPV vaccination was high (ranging from 66% to 97%), there was a high degree of heterogeneity (overall I2 = 96.4%) between studies and much of this heterogeneity may be attributable to age of intended recipient. Physicians were more likely to recommend vaccination to older girls. The proportion of physicians likely to vaccinate were 73% (95% CI: 68%-78%), 89% (95% CI: 76%-95%), and 95% (95% CI: 84%-98%) for recipients aged less than 14 years, 14–17 years, and greater than 17 years, respectively (p=0.0014). This runs counter to the ACIP guidelines, recommending routine HPV vaccination of females aged 11 or 12 years or catch-up vaccination in women 13–26 years of age (Markowitz et al., 2007). Additionally, as we found physician recommendation was a strong predictor of vaccination intention both in parents and individuals, a campaign to increase vaccination rates might better focus on increasing physician' early, strong recommendations to follow the appropriate vaccination schedule.

Finally, study three showed that there are similarities between the Utah population and the general U.S. population regarding factors related to vaccine intention, e.g., physician recommendation is very influential. However, there are particularities of the population of Utah that might require further message tailoring and this study helped to inform those future interventions. Particularly, age, marital status, religious practice, and education level were significantly associated with vaccine intention.

The next steps following these studies are to create a community intervention targeted both toward receptive individuals, as identified by our studies, and also, and perhaps more importantly, toward community physicians in Utah.

Preliminary interventions to increase vaccination rates in Utah could target increasing Utah physician's likelihood of recommending the HPV vaccine. Initial steps would include assessing baseline physicians' intention to recommend the vaccine and also to identify physicians with a very high likelihood of recommending the vaccine, i.e., the positive-deviant physician recommenders. This physician group could provide insights into scripting that could be used to increase vaccination likelihood in their peer physicians. Follow-up would then be performed to evaluate the impact of the intervention on increased physician intention to vaccinate and, subsequently, increased HPV vaccination rates in Utah.

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